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(54) Title: HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAs ENCODING THESE PROTEINS

(57) Abstract: The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, transformed eukaryotic cells expressing these DNAs and antibodies directed to these proteins.

DESCRIPTION

Human Proteins Having Hydrophobic

Domains and DNAs Encoding These Proteins

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TECHNICAL FIELD

The present invention relates to human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, eukaryotic 10 expressing these DNAs and antibodies directed to these proteins. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies directed to these proteins. The human cDNAs of the present invention can be utilized as probes for genetic diagnosis and gene sources for gene therapy. Furthermore, 15 the cDNAs can be utilized as gene sources for producing the proteins encoded by these cDNAs in large quantities. Cells into which these genes are introduced to express secretory proteins or membrane proteins in large quantities can be utilized for detection of the corresponding receptors or 20 ligands, screening of novel small molecule pharmaceuticals and the like. The antibodies of the present invention can be utilized for the detection, quantification, purification and the like of the proteins of the present invention.

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BACKGROUND ART

Cells secrete many proteins extracellularly. These secretory proteins play important roles in the proliferation differentiation induction, the control, the transport, the biophylaxis, and the like of the cells. Unlike intracellular proteins, the secretory proteins exert their actions outside the cells. Therefore, they can be administered in the intracorporeal manner such as the so that they possess hidden injection or the drip, potentialities as pharmaceuticals. In fact, a number of human secretory proteins such as interferons, interleukins, erythropoietin, thrombolytic agents and the like addition, In pharmaceuticals. employed as currently secretory proteins other than those described above are undergoing clinical trials for developing their use as pharmaceuticals. It is believed that the human cells produce many unknown secretory proteins. Availability of these secretory proteins as well as genes encoding them expected to lead to development of novel pharmaceuticals utilizing them.

On the other hand, membrane proteins play important roles, as signal receptors, ion channels, transporters and the like in the material transport and the signal transduction through the cell membrane. Examples thereof include receptors for various cytokines, ion

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channels for the sodium ion, the potassium ion, the chloride ion and the like, transporters for saccharides and amino acids and the like. The genes for many of them have already been cloned. It has been clarified that abnormalities in these membrane proteins are involved in a number of previously cryptogenic diseases. Therefore, discovery of a new membrane protein is expected to lead to elucidation of the causes of many diseases, so that isolation of new genes encoding the membrane proteins has been desired.

Heretofore, due to difficulty in the purification from human cells, many of these secretory proteins and membrane proteins have been isolated by genetic approaches. A general method is the so-called expression cloning method, in which a cDNA library is introduced into eukaryotic cells to express cDNAs, and the cells secreting, or expressing on the surface of membrane, the protein having the activity of interest are then screened. However, only genes for proteins with known functions can be cloned by using this method.

protein possesses at least one hydrophobic domain within the protein. After synthesis on ribosomes, such domain works as a secretory signal or remains in the phospholipid membrane to be entrapped in the membrane. Accordingly, if the existence of a highly hydrophobic domain is observed in the amino acid sequence of a protein encoded by a cDNA when the

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whole base sequence of the full-length cDNA is determined, it is considered that the cDNA encodes a secretory protein or a membrane protein.

5 OBJECTS OF INVENTION

The main object of the present invention is to provide novel human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, transformed eukaryotic cells that are capable of expressing these DNAs and antibodies directed to these proteins. This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description with reference to the accompanying drawings.

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SUMMARY OF INVENTION

As the result of intensive studies, the present inventors have successfully cloned cDNAs encoding proteins having hydrophobic domains from the human full-length cDNA bank, thereby completing the present invention. Thus, the present invention provides a human protein having hydrophobic domain(s), namely a protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100 and 121 to 130. Moreover, the present invention provides a DNA

encoding said protein, exemplified by a cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID NOS: 11 to 30, 41 to 60, 71 to 90, 101 to 120 and 131 to 150, an expression vector that is capable of expressing said DNA by in vitro translation or in eukaryotic cells, a transformed eukaryotic cell that is capable of expressing said DNA and of producing said protein and an antibody directed to said protein.

10 BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03171.

Fig. 2 illustrates the

hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03424.

Fig. 3 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03444.

Fig. 4 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03478.

Fig. 5 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03499.

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	hydrophobicity/hydrophyd	philicity prof	ile of the protein e	ncoqea
	by clone HP03500.			
	Fig.		illustrates	the
5	hydrophobicity/hydro		file of the protein e	ncoded
	by clone HP10691.			
	Fig.	_	illustrates	the
	hydrophobicity/hydro	philicity pro	file of the protein e	encoded
	by clone HP10703.			
10	- Fig.	9	illustrates	- the
10	hydrophobicity/hydro	ophilicity pro	file of the protein	encoded
	by clone HP10711.		2.2	
	Fig.	10	illustrates	the
	hydrophobicity/hydr	ophilicity pro	ofile of the protein	encoded
15	by clone HP10712.			.
	- Fig.	11	illustrates	the
	hydrophobicity/hydr	ophilicity pr	ofile of the protein	encoded
	by clone HP03010.		:	
	Fig.	12	illustrates :	the
20	hydrophobicity/hyd:	rophilicity pr	ofile of the protein	encoded
	by clone HP03576.			
	Fig.	13	illustrates	the
	hydrophobicity/hyd	rophilicity p	cofile of the protein	encoded
25	Fig.	14	illustrates	# the

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the

hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03612.

Fig. 15 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10407.

Fig. 16 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10713.

illustrates

hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10714.

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Fig.

Fig. 18 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10716.

Fig. 19 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10717.

Fig. 20 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10718.

Fig. 21 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03745.

Fig. 22 illustrates the 25 hydrophobicity/hydrophilicity profile of the protein encoded

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by clone HP03747.

illustrates 🚟 23 Fig. hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10719.

illustrates the 24 Fig. 5 hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10720.

illustrates the 25 Fig. hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10721.

the illustrates 26 Fig. hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10725.

illustrates 27 Fig. hydrophobicity/hydrophilicity profile of the protein encoded 15 . by clone HP10727.

the illustrates 28 Fig. hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10728.

29 illustrates Fig. 20 hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10730.

the illustrates 30 Fig. hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10742.

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		Fig. 31	illustrates	the
		hydrophobicity/hydrophilicit	y profile of the protein enc	oded
		by clone HP03800.		
		Fig. 32	illustrates	the
	5	hydrophobicity/hydrophilicit	y profile of the protein enco	oded
		by clone HP03831.		
		Fig. 33	illustrates	the
		hydrophobicity/hydrophilicity	y profile of the protein enco	oded
	•	by clone HP03879.		
	10	Fig. 34	illustrates	the
		hydrophobicity/hydrophilicity	y profile of the protein enco	oded
		by clone HP03880.		
		Fig. 35	illustrates	the
		hydrophobicity/hydrophilicity	profile of the protein enco	oded
	15	by clone HP10704.	÷	
		Fig. 36	illustrates	the
		hydrophobicity/hydrophilicity	profile of the protein enco	ded
		by clone HP10715.		
	,	Fig. 37	illustrates	the
	20	hydrophobicity/hydrophilicity	profile of the protein enco	ded
		by clone HP10724.		
		Fig. 38	illustrates	the
		hydrophobicity/hydrophilicity	•	
		by clone HP10733.	•	
• •	2.5	Fig 39	illustrates	the

	hydrophobicity/hydrophil	icity	profile	of th	e prote	in e	ncoded	
	by clone HP10734.							
	Fig.	40	i	llust	rates		the	
	hydrophobicity/hydrophil	icity	profile	of th	ne prote	in e	ncoded	
5	by clone HP10756.	-			-		:	
	Fig.	41	i	llust	rates		the	
	hydrophobicity/hydrophil	icity	profile	of th	ne prote	in e	encoded	
	by clone HP03670.			٠		•		
	Fig.	42	i	llust	rates .		the	:
10	hydrophobicity/hydrophil	icity	profile	of the	he prote	ein e	encoded	l
	by clone HP03688.						13° 150 -	
	Fig.	43	· i	llust	rates	•	the	<u> </u>
	hydrophobicity/hydrophil	Licity	profile	of t	he prote	ein (encoded	ì
	by clone HP03825						*	
15	Fig.	44	j	illust	rates .	,	: the)
	hydrophobicity/hydrophi	licity	profile	of t	he prote	ein	encodeo	Ĺ
	by clone HP03877.							
	Fig.	45	. :	illust	crates		the	9
	hydrophobicity/hydrophi	licity	y profile	e of t	he prot	ein	encode	Ĺ
20	by clone HP10765.			-				
	Fig.	46		illust	trates		th	е
	hydrophobicity/hydrophi	licit	y profile	e of t	the prot	ein	encode	d
	by clone HP10766.			• • • •				
	Fig.	47		illus	trates		th	e
25	hydrophobicity/hydrophi	licit	y profile	e of 1	the prot	ein	encode	d

by clone HP10770.

Fig. 48 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10772.

Fig. 49 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10773.

Fig. 50 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10776.

DETAILED DESCRIPTION OF THE INVENTION

The proteins of the present invention can be obtained, for example, by a method for isolating proteins 15 from human organs, cell lines or the like, a method for preparing peptides by the chemical synthesis based on the amino acid sequences of the present invention, or a method for producing proteins by the recombinant DNA technology using the DNAs encoding the hydrophobic domains of the 20 present invention. Among these, the method for producing proteins by the recombinant DNA technology is preferably employed. For example, the proteins can be expressed in vitro by preparing an RNA by in vitro transcription from a vector having the cDNA of the present invention, and then carrying out in vitro translation using this RNA as a 25

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region into a suitable expression vector by the method known in the art may lead to expression of a large amount of the encoded protein in prokaryotic cells such as Escherichia coli, Bacillus subtilis, etc., and eukaryotic cells such as yeasts, insect cells, mammalian cells, etc.

In the case where the protein of the present invention is produced by expressing the DNA by in vitro translation, the protein of the present invention can be produced in vitro by incorporating the translated region of this cDNA into a vector having an RNA polymerase promoter, and then adding the vector to an in vitro translation system such as a rabbit reticulocyte lysate or a wheat germ extract, which contains an RNA polymerase corresponding to promoter. The RNA polymerase promoters are exemplified by T7, T3, SP6 and the like. The vectors containing promoters for these RNA polymerases are exemplified by pKA1, pCDM8, pT3/T7 18, pT7/3 19, pBluescript II and the like. Furthermore, the protein of the present invention can be expressed in the secreted form or the form incorporated in the microsome membrane when a canine pancreas microsome or the like is added to the reaction system.

In the case where the protein of the present invention is produced by expressing the DNA in a microorganism such as Escherichia coli etc., a recombinant

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expression vector in which the translated region of the cDNA of the present invention is incorporated into an expression vector having an origin which is capable of replicating in the microorganism, a promoter, a ribosome-binding site, a cDNA-cloning site, a terminator and the like is constructed. After transformation of the host cells with this expression vector, the resulting transformant is cultivated, whereby the protein encoded by the cDNA can be produced in large quantities in the microorganism. In this case, a protein fragment containing any translated region can be obtained by adding an initiation codon and a termination codon in front of and behind the selected translated region to express the protein. Alternatively, the protein can be expressed as a fusion protein with another protein. Only the portion of the protein encoded by the cDNA can be obtained by cleaving this fusion protein with a suitable protease. The expression vectors for Escherichia coli are exemplified by the pUC series, pBluescript II, the pET expression system, the pGEX expression system and the like.

In the case where the protein of the present invention is produced by expressing the DNA in eukaryotic cells, the protein of the present invention can be produced as a secretory protein, or as a membrane protein on the surface of cell membrane, by incorporating the translated region of the cDNA into an expression vector for eukaryotic

cells that has a promoter, a splicing region, a poly(A) addition site and the like, and then introducing the vector into the eukaryotic cells. The expression vectors are exemplified by pKA1, pED6dpc2, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vectors, pRS, pYES2 and the like. Examples of eukaryotic cells to be used in general include mammalian cultured cells such as monkey kidney COS7 cells, Chinese hamster ovary CHO cells and the like, budding yeasts, fission yeasts, silkworm cells, Xenopus oocytes and the like. Any eukaryotic cells may be used as long as they are capable of expressing the proteins of the present invention. The expression vector can be introduced into the eukaryotic cells by using a method known in the art such as the electroporation method, the calcium phosphate method, the liposome method, the DEAE-dextran method and the like.

After the protein of the present invention is expressed in prokaryotic cells or eukaryotic cells, the protein of interest can be isolated and purified from the culture by a combination of separation procedures known in the art. Examples of the separation procedures include treatment with a denaturing agent such as urea or a detergent, sonication, enzymatic digestion, salting-out or centrifugation, solvent precipitation, dialysis, ultrafiltration, gel filtration, SDS-PAGE, isoelectric 25 focusing, ion-exchange chromatography, hydrophobic

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chromatography, affinity chromatography, reverse phase chromatography and the like.

The proteins of the present invention also include peptide fragments (of 5 amino acid residues containing any partial amino acid sequences in the amino acid sequences represented by SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100 and 121 to 130. These peptide fragments can be utilized as antigens for preparation of antibodies. Among the proteins of the present invention, those having the signal sequences are secreted in the form of mature proteins after the signal sequences are removed. Therefore, these mature proteins shall come within the scope of the protein of the present invention. The N-terminal amino acid sequences of the mature proteins can be easily determined by using the method for the determination of cleavage site of a signal sequence [JP-A 8-187100]. Furthermore, some membrane proteins undergo the processing on the cell surface to be converted to the secreted forms. Such proteins or peptides in the secreted forms shall also come within the scope of the protein of the present invention. In the case where sugar chain-binding sites are present in the amino acid sequences of the proteins, expression of the proteins in appropriate eukaryotic cells affords the proteins to which sugar chains are added. Accordingly, such proteins or peptides to which sugar chains are added shall also come

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within the scope of the protein of the present invention.

The DNAs of the present invention include all the DNAs encoding the above-mentioned proteins. These DNAs can be obtained by using a method for chemical synthesis, a method for cDNA cloning and the like.

The cDNAs of the present invention can be cloned, for example, from cDNA libraries derived from the human cells. The cDNAs are synthesized by using poly(A)* RNAs extracted from human cells as templates. The human cells may be cells delivered from the human body, for example, by the operation or may be the cultured cells. The cDNAs can be synthesized by using any method such as the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-(1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J., Gene 25: 263-269 (1983)] and the like. However, it is desirable to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner. In addition, commercially available human cDNA libraries can be utilized. The cDNAs of the present invention can be libraries by synthesizing CDNA from the cloned oligonucleotide on the basis of base sequences of any portion in the cDNA of the present invention and screening the cDNA libraries using this oligonucleotide as a probe for colony or plaque hybridization according to a method known

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in the art. In addition, the cDNA fragments of the present invention can be prepared from an mRNA isolated from human cells by the RT-PCR method in which oligonucleotides which hybridize with both termini of the cDNA fragment of interest are synthesized, which oligonucleotides are then used as the primers.

The **CDNAs** of the present invention characterized in that they comprise any one of the base sequences represented by SEQ ID NOS: 11 to 20, 41 to 50, 71 to 80, 101 to 110 and 131 to 140 or the base sequences 10 represented by SEQ ID NOS: 21 to 30, 51 to 60, 81 to 90, 111 to 120 and 141 to 150. Tables 1 and 2 summarizes the clone number (HP number), the cell from which the cDNA clone was obtained, the total number of bases of the cDNA, and the number of the amino acid residues of the encoded protein, 15 for each of the cDNAs.

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Table 1

Table	Ţ.	 	· · · ·	<u> </u>	<u> </u>	
SEQ	ID	NO.	HP	Cell	Number of bases	Number of amino acid residues
1,	11	, 21	HP03171	Thymus	2042	267
2,	12	, 22	HP03424	Liver	1433	419
3,	13	, 23	HP03444	Kidney	. 1917 .	415
4,	14	, 24	HP03478	Umbilical cord blood	2258	380
5,	15	, 25	HP03499	Kidney	1973	585
6,	16	, 26	HP03500	kidney	1606:	331
7,	17	, 27	HP10691	Umbilical cord blood	2380	345
8,	18	, 28	HP10703	Kidney	2017	89
9,	19	, 29	HP10711	Kidney	1606	406
10,	20	, 30	HP10712	Kidney	1695	192
31,	41	, 51	HP03010	Kidney	1551	377
32,	42	, 52	HP03576	Kidney	1713	81
33,	43	, 53	-HP03611	Kidney	1758	487
34,	·44	, 54	HP03612	Kidney	1550	375
35,	45	, 55	HP10407	Stomach cancer	1485	350
36,	46	, 56	HP10713	Kidney	2694	667
37,	47	, 57	HP10714	Umbilical cord blood	3297	464
38,	48	, 58	HP10716	Umbilical cord blood	2126	470
39,	49	, 59	HP10717	Kidney	1781	243
40,	50	, 60	HP10718	Umbilical cord blood	1788	270
61,	71	, 81	HP03745	Kidney	1376	389
62,	72	, 82	HP03747	Umbilical cord blood	2392	348
63,	73	, 83	HP10719	Kidney	1416	261
64,	74	, 84	HP10720	Kidney	1347	222
65,	75	85	HP10721	Kidney	2284	183

Table 2

SEC) ID 1	NO	HP number	Cell	Number of bases	Number of amino acid residues
66,	76,	86	HP10725	Kidney	1737	262
67,	77,	87	HP10727	Umbilical cord blood	1556	168
68,	78,	88	HP10728	Umbilical cord blood	1855	243
69,	79,	89	HP10730	Umbilical cord blood	2530	428
70,	80,	90	HP10742	Umbilical cord blood	1911	283
91,	101,	111	HP03800	Umbilical cord blood	1633	476
92,	102,	112	HP03831	Kidney	1095	226
93,	103,	113	HP03879	Kidney	1602	305
94,	104,	114	HP03880	Kidney	897	227
. 95,	105,	115	HP10704	Kidney	1866	441
96,	106,	116	. HP10715	Umbilical cord blood	2198	265
97,	107,	117	HP10724	Umbilical cord blood	2180	208
98,	108,	118	HP10733	Umbilical cord blood	1527	400
99,	109,	119	HP10734	Umbilical cord blood	1905	192
100,	110,	120	HP10756	Kidney	998	260
121,	131,	141	HP03670	Umbilical cord blood	1622	337
122,	132,	142	HP03688	Umbilical cord blood	2475	236
123,	133,	143	HP03825	Kidney	1739	560
124,	134,	144	HP03877	Kidney	2005	406
125,	135,	145	HP10765	Umbilical cord blood	1558	453
126,	136,	146	HP10766	Kidney	1005	59
127,	137,	147	HP10770	Kidney	969	210
128,	138,	148	HP10772	Kidney	1241	165
129,	139,	149	HP10773	Kidney	1174	162
130,	140,	150	HP10776	Kidney	1012	221

The same clones as the cDNAs of the present invention can be easily obtained by screening the cDNA libraries constructed from the human cell lines or human

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tissues utilized in the present invention using an oligonucleotide probe synthesized on the basis of the base sequence of the cDNA provided in any one of SEQ ID NOS: 11 to 30, 41 to 60, 71 to 90, 101 to 120 and 131 to 150.

In general, the polymorphism due to the individual differences is frequently observed in human genes. Accordingly, any cDNA in which one or plural nucleotides are added, deleted and/or substituted with other nucleotides in SEQ ID NOS: 11 to 30, 41 to 60, 71 to 90, 101 to 120 and 131 to 150 shall come within the scope of the present invention.

Similarly, any protein in which one or plural amino acids are added, deleted and/or substituted with other amino acids resulting from the above-mentioned changes shall come within the scope of the present invention, as long as the protein possesses the activity of the protein having any one of the amino acid sequences represented by SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100 and 121 to 130.

The cDNAs of the present invention also include cDNA fragments (of 10 bp or more) containing any partial base sequence in the base sequences represented by SEQ ID NOS: 11 to 20, 41 to 50, 71 to 80, 101 to 110 and 131 to 140 or in the base sequences represented by SEQ ID NOS: 21 to 30, 51 to 60, 81 to 90, 111 to 120 and 141 to 150. Also, DNA fragments consisting of a sense strand and an anti-sense strand shall come within this scope. These DNA fragments can

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be utilized as the probes for the genetic diagnosis.

The antibody of the present invention can be obtained from a serum after immunizing an animal using the protein of the present invention as an antigen. A peptide that is chemically synthesized based on the amino acid sequence of the present invention and a protein expressed in eukaryotic or prokaryotic cells can be used as an antigen. Alternatively, an antibody can be prepared by introducing the above-mentioned expression vector for eukaryotic cells into the muscle or the skin of an animal by injection or by using a gene gun and then collecting a serum therefrom (JP-A 7-313187). Animals that can be used include a mouse, a rat, a rabbit, a goat, a chicken and the like. A monoclonal antibody directed to the protein of the present invention can be produced by fusing B cells collected from the spleen of the immunized animal with myelomas to generate hybridomas.

In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for

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introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express for analysis, characterization protein recombinant therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of differentiation or development or in disease states); "as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA patients to identify potential sequences in disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein

(such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris t al., Cell '75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-10 throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding 15 protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can . 20 be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or 2.5 agonists of the binding interaction.

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Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation

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Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Marqulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 25 137:3494-3500, 1986; Bertagnolli et al., J. Immunol.

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145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

- Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.
- Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology.

 J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6-Nordan, R. In Current Protocols in Immunology. J.E.e.a.

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Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 -Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies . 20 in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

25 Immune Stimulating or Suppressing Activity

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A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania malaria spp. and various fungal infections such candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune

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pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. immune suppression is desired in which conditions, (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an may progress or already in response immune response. The induction of immune an preventing the be inhibited by functions of activated T cells may inducing specific suppressing T cell responses or by tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigenspecific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by

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the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. tissue transplants, rejection of Typically, in transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant.

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Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases.

Many autoimmune disorders are the result of inappropriate

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activation of T cells that are reactive against self tissue and which promote the production of cytokines autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor: ligand interactions of B lymphocyte antiqens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents induce antigen-specific tolerance of may autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can ... be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy.

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Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte

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antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a

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cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated invariant chain, can such as the protein, cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19;

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Chapter 7, Immunologic studies in Humans); Herrmann et al. Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 5 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. 10 Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

for T-cell-dependent immunoglobulin Assays responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Thl and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E.

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Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-In Vitro assays for Interscience (Chapter 3, Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 20 1990.

> Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those

described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or

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erythroid cells; in supporting the growth and proliferation and granulocytes cells such as myeloid monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting proliferation of megakaryocytes and growth the consequently of platelets thereby allowing prevention or disorders such as various platelet treatment of thrombocytopenia, and generally for use in place of or complementary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the abovementioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without and paroxysmal nocturnal aplastic anemia limitation, hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or marrow conjunction with bone (i.e., ex-vivo in progenitor cell transplantation or with peripheral transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

2.5. Suitable: assays: for proliferation e and

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differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

10 Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In Culture of Hematopoietic Cells. R.I. 15 Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New 20 York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New 25 York, NY. 1994; Long term bone marrow cultures in the

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presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth

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repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or

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ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may .provide an environment to attract tendon or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, differentiation of progenitors of tendonligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be in the treatment of tendinitis, carpal tunnel useful The defects. syndrome and other tendon ligament or compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be neural cells and for proliferation of for useful regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nerve injuries, system, such as peripheral nervous peripheral neuropathy and localized neuropathies, central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic

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lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

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proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

25 A protein of the present invention may also be

useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. W095/16035 (bone, cartilage, tendon); International Patent Publication No. W095/05846 (nerve, neuronal); International Patent Publication No. W091/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of

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follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et

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al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, and/or endothelial cells. epithelial eosinophils, Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized For example, attraction of lymphocytes, infections. monocytes or neutrophils to tumors or sites of infection may 15 result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell

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chemotaxis.

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The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other

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hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke)).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen

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presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity

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may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cellcell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inhibiting promoting or inflammatory process, extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, rejection, nephritis, complement-mediated hyperacute cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly

(such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body for example, breast size orshape (such as, augmentation or diminution, change in bone form or shape); effecting biorhythms or cardiac cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or

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nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), (including depressive disorders), and violent depression behaviors; providing analgesic effects or other reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulinlike activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

Examples

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The present invention is specifically illustrated in more detail by the following Examples, but Examples are not intended to restrict the present invention. The basic procedures with regard to the recombinant DNA and the enzymatic reactions were carried out according to the literature ["Molecular Cloning. A Laboratory Manual", Cold

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Spring Harbor Laboratory, 1989]. Unless otherwise stated, restriction enzymes and various modifying enzymes to be used were those available from Takara Shuzo. The buffer compositions and the reaction conditions for each of the enzyme reactions were as described in the attached instructions. The cDNA synthesis was carried out according to the literature [Kato, S. et al., Gene 150: 243-250 (1994)].

(1) Selection of cDNAs Encoding Proteins Having

10 Hydrophobic Domains

Human liver cDNA library (WO 98/21328) and human stomach cancer cDNA library (WO 98/21328), as well as the cDNA libraries constructed from human kidney mRNA (Clontech), human thymus mRNA (Clontech) and human umbilical cord blood mRNA were used as cDNA libraries.

Full-length cDNA clones were selected from the respective libraries and the whole base sequences thereof were determined to construct a homo-protein cDNA bank consisting of the full-length cDNA clones. The hydrophobicity/hydrophilicity profiles were determined for the proteins encoded by the full-length cDNA clones registered in the homo-protein cDNA bank by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Biol. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic domain. A clone that has a hydrophobic region

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being assumed as a secretory signal or a transmembrane domain in the amino acid sequence of the encoded protein was selected as a clone candidate.

(2) Protein Synthesis by In Vitro Translation

The plasmid vector bearing the cDNA of the present invention was used for in vitro transcription/translation with a T_NT rabbit reticulocyte lysate kit (Promega). In this case, [35S]methionine was added to label the expression product with a radioisotope. Each of the reactions was carried out according to the protocols attached to the kit. Two micrograms of the plasmid was subjected to the reaction at 30°C for 90 minutes in the reaction solution of a total volume of 25 µl containing 12.5 µl µ of T_NT rabbit reticulocyte lysate, 0.5 µl of a buffer solution (attached to the kit), 2 µl of an amino acid mixture (without methionine), 2 μ l of [35S]methionine (Amersham) (0.37 MBq/ μ l), 0.5 µl of T7 RNA polymerase, and 20 U of RNasin. experiment in the presence of a membrane system was carried out by adding $2.5~\mu l$ of a canine pancreas microsome fraction (Promega) to the reaction system. To 3 µl of the reaction solution was added 2 µl of the SDS sampling buffer (125 mM Tris-hydrochloride buffer, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue and 20% glycerol) and the resulting mixture was heated at 95°C for 3 minutes and then subjected to SDS-polyacrylamide gel electrophoresis.

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The molecular weight of the translation product was determined by carrying out the autoradiography.

(3) Expression in COS7

Escherichia coli cells harboring the expression vector for the protein of the present invention were cultured at 37°C for 2 hours in 2 ml of the 2 x YT culture medium containing 100 μ g/ml of ampicillin, the helper phage M13K07 (50 μ 1) was added thereto, and the cells were then cultured at 37°C overnight. Single-stranded phage particles were obtained by polyethylene glycol precipitation from a supernatant separated by centrifugation. The particles were suspended in 100 μ l of 1 mM Tris-0.1 mM EDTA, pH 8 (TE).

The cultured cells derived from monkey kidney, COS7, were cultured at 37°C in the presence of 5% CO₂ in the Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum. 1 x 10⁵ COS7 cells were inoculated into a 6-well plate (Nunc, well diameter: 3 cm) and cultured at 37°C for 22 hours in the presence of 5% CO₂. After the medium was removed, the cell surface was washed with a phosphate buffer solution followed by DMEM containing 50 mM Trishydrochloride (pH 7.5) (TDMEM). A suspension containing 1 µl of the single-stranded phage suspension, 0.6 ml of the DMEM medium and 3 µl of TRANSFECTAMTM (IBF) was added to the cells and the cells were cultured at 37°C for 3 hours in the presence of 5% CO₂. After the sample solution was removed,

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the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf serum was added, and the cells were cultured at 37°C for 2 days in the presence of 5% CO₂. After the medium was exchanged for a medium containing [35S]cysteine or [35S]methionine, the cells were cultured for one hour. After the medium and the cells were separated each other by centrifugation, proteins in the medium fraction and the cell membrane fraction were subjected to SDS-PAGE.

(4) Preparation of Antibodies

A plasmid vector containing the cDNA of the present invention was dissolved in a phosphate buffer solution (PBS: 145 mM NaCl, 2.68 mM KCl, 8.09 mM Na₂HPO₄, 2 mM KH,PO, pH 7.2) to a concentration of 2 µg/µl. 25 µl each (a total of 50 µl) of the thus-prepared plasmid solution in PBS was injected into the right and left musculi quadriceps femoris of three mice (ICR line) using a 26 guage needle. After similar injections were repeated for one month at intervals of one week, blood was collected. The collected blood was stored at 4°C overnight to coagulate the blood, and then centrifuged at 8,000 x g for five minutes to obtain a supernatant. NaN, was added to the supernatant to a concentration of 0.01% and the mixture was then stored at 4°C. The generation of an antibody was confirmed immunostaining of COS7 cells into which the corresponding vector had been introduced or by Western blotting using a

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cell lysate or a secreted product.

(5) Clone Examples

<HP03171> (SEQ ID NOS: 1, 11 and 21)

Determination of the whole base sequence of the cDNA insert of clone HP03171 obtained from cDNA library of human thymus revealed the structure consisting of a 90-bp 5'-untranslated region, a 804-bp ORF, and a 1148-bp 3'untranslated region. The ORF encodes a protein consisting of 267 amino acid residues and there existed one putative depicts transmembrane domain. Figure 1 hydrophobicity/hydrophilicity profile, obtained by the Kyteof the present protein. In Doolittle method, translation resulted in formation of a translation product of 34 kDa that was somewhat larger than the molecular weight of 30,234 predicted from the ORF. In this case, 7the addition of a microsome led to the formation of a product of 38 kDa. In addition, there exists in the amino acid sequence of this protein one site at which N-glycosylation may occur (Asn-Thr-Thr at position 169).

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to chicken putative transmembrane protein E3-16 (Accession No. AAB70816). Table 3 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and chicken putative

transmembrane protein E3-16 (GG). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 43.0% in the entire region.

Table 3

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HP RATRRINKRGAKNCNAIRHFENTFVVETLICGVV

* ** ** * ** ***** * *****

GG KEAMKGIQKREAVNCRKIRHFENRFAMETLICEQ

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AL036384) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP03424> (SEQ ID NOS: 2, 12 and 22)

Determination of the whole base sequence of the CDNA insert of clone HP03424 obtained from cDNA library of human liver revealed the structure consisting of a 4-bp 5'-untranslated region, a 1260-bp ORF, and a 169-bp 3'-untranslated region. The ORF encodes a protein consisting of 419 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the inner portion. Figure 2 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 50 kDa that was somewhat larger than the molecular weight

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of 46,375 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 54 kDa. In addition, there exist in the amino acid sequence of this protein six sites at which N-glycosylation may occur (Asn-Ala-Ser at position 29, Asn-Val-Thr at position 40, Asn-Cys-Thr at position 112, Asn-Lys-Ser at position 135, Asn-Ile-Ser at position 172 and Asn-Phe-Ser at position 189). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from aspartic acid at position 28.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to Drosophila melanogaster GOLIATH protein (Accession No. Q06003). Table 4 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Drosophila melanogaster GOLIATH protein (DM). Therein, the marks of -, *, and represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 40.8% in the intermediate region of 218 amino acid residues.

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		Table 4	
		HP MSCAGRAGPARLAALALLTCSLWPARADNASQEYYTALINVTVQEPGRGAPLTFRIDRGR	
	5	HP YGLDSPKAEVRGQVLAPLPLHGVADHLGCDPQTRFFVPPNIKQWIALLQRGNCTFKEKIS	:
		HP RAAFHNAVAVVIYNNKSKEEPVTMTHPGTGDIIAVMITELRGKDILSYLEKNISVQMTIA	
		* ** *.*. *.*	
		DM MQLEKMQIKGKTRNIAAVITYQNIGQDLSLTLDKGYNVTISII	
	10		177
		HP VGTRMPPKNFSRGSLVFVSISFIVLMIISSAWLIFYFIQKIRYTNARDRNQRRLGDAA	
		* **.*.****** *. *****.*****.	
		DM EGRRGVRTISSLNRTSVLFVSISFIVDDILCWLIFYYIQRFRYMQAKDQQSRNLCSVT	
			. •
	15	HP KKAISKLTTRTVKKGDKETDPDFDHCAVCIESYKQNDVVRILPCKHVFHKSCVDPWLSEH	a ;
		**** *. * * * * * * * * * * * * * * * *	
		DM KKAIMKIPTKTGKFSD-EKDLDSDCCAICIEAYKPTDTIRILPCKHEFHKNCIDPWLIEH	
		HP CTCPMCKLNILKALGIVPNLPCTDNVAFDMERLTRTQAVNRRSALGDLAGDNSLGLEPLR	
	20	******* ** * *	337
		DM RTCPMCKLDVLKFYGYVVGDQIYQTPSPQHTAPIASIEEVPVIVVAVPHGPQPLQPLQ	
		en la companya di mangantan di m	
. •		HP TSGISPLPQDGELTPRTGEINIAVTKEWFIIASFGLLSALTLCYMIIRATASLNANEVEW	
		.**	
	25	DM ASNMSSFAPSHYFQSSRSPSSSVQQQLAPLTYQPHPQQAASERGRRNSAPATMPHAITAS	= <u>C</u>

HP F

DM HQVTDV

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA082118) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03444> (SEQ ID NOS: 3, 13 and 23)

15 Determination of the whole base sequence of the cDNA insert of clone HP03444 obtained from cDNA library of human kidney revealed the structure consisting of a 209-bp 5'-untranslated region, a 1248-bp ORF, and a 460-bp 3'untranslated region. The ORF encodes a protein consisting of 20 415 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 3 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 43 kDa that was somewhat smaller than the molecular 25

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weight of 45,691 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 42 kDa. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from glutamine at position 24.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human type I procollagen C-proteinase enhancer protein (Accession No. BAA23281). Table 5 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human type I procollagen C-proteinase enhancer protein (CP). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 43.6% in the entire region.

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20 Table 5

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HP MRGANAWAPLCLLLAAATQLSRQQSPERPVFTCGGILTGESGFIGSEGFPGVYP

* **. * * **** *** . . *****. . **

CP MLPAATASLLGPLLTACALLPFA-Q-GQTPNYTRPVFLCGGDVKGESGYVASEGFPNLYP

	HP PNSKCTWKITVPEGKVVVLNFRFIDLESDNLCRYDFVDVYNGH-ANGQRIGRFCGTFRPG
	. *. *. ****. * *. *** . *** * ***. ******
	CP PNKECIWTITVPEGQTVSLSFRVFDLELHPACRYDALEVFAGSGTSGQRLGRFCGTFRPA
5	HP ALVSSGNKMMVQMISDANTAGNGFMAMFSAAEPNERGDQYCGGLLDRPSGSFKTPNWPDR
	.********
	CP PLVAPGNQVTLRMTTDEGTGGRGFLLWYSGRATSGTEHQFCGGRLEKAQGTLTTPNWPES
	HP DYPAGVTCVWHIVAPKNQLIELKFEKFDVERDNYCRYDYVAVFNGGEVNDARRIGKYCGD
10	***. *. * ***. ** . *. *. **. **. *. *.
	CP DYPPGISCSWHIIAPPDQVIALTFEKFDLEPDTYCRYDSVSVFNGAVSDDSRRLGKFCGD
	HP SPPAPIVSERNELLIQFLSDLSLTADGFIGHYIFRPKKLPTTTE
	. ** ** ****. **. **** . * *
15	CP AVPGSISSEGNELLVQFVSDLSVTADGFSASYKTLPRGTAKEGQGPGPKRGTEPKVKLPP
	HP QPVTTTFPVTTGLKTTVALCQQKCRRTGTLEGNYCSSDFVLAGTVITTITRDG-SLHATV
	*
	CP KSQPPEKTEESPSAPDAPTCPKQCRRTGTLQSNFCASSLVVTATVKSMVREPGEGLAVTV
20 .	
	HP SIINIYKEGNLAIQQAGKNMSARLTVVCKQCPLLRRGLNYIIMGQVGEDGRGKIM-PNSF
	.. **. *
	CP SLIGAYKTGGLDLPSPPTGASLKFYVPCKQCPPMKKGVSYLLMGQV-EENRGPVLPPESF
3 E	HD TIMEKTKNOKI I DAI KNKOC

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4.1.3

CP VVLHRPNQDQILTNLSKRKCPSQPVRAAASQD

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. D78874) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03478> (SEQ ID NOS: 4, 14 and 24)

Determination of the whole base sequence of the cDNA insert of clone HP03478 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 224-bp 5'-untranslated region, a 1143-bp ORF, and a 891-bp 3'-untranslated region. The ORF encodes a protein consisting of 380 amino acid residues and there existed five putative transmembrane domains. Figure 4 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the

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protein was similar to Halocynthia roretzi HrPET-1 protein (Accession No. BAA81907). Table 6 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Halocynthia roretzi HrPET-1 protein (HR). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 36.8% in the entire region.

Table 6

HP MLQTLYDYFWWERLWLPVNLTWADLEDRDGRVYAKASDLYITLPLALLFLIVRYFFEL 15 HR MDLLMDLYHWFWNEKFWLPQNLTWEDLKRTEEKQFGETRDLWLTFPLCITVLCIRFSVEK HP YVATPLAALLNIKEKTRLRAPPNATLEHFYLTSGKQPKQVEVELLSRQSGLSGRQVERWF HR GIARPLGKWLNLSERLHTPPRENIVLEKVYKTITRKPNYSQVEDLCKQTGWRKHEINVWF 20 The state of the s HP RRRRNQDRPSLLKKFREASWRFTFYLIAFIAGMAVIVDKPWFYDMKKVWEGYPIQSTIPS HR RKKNLVGRPTTLTKFQETFWRFAFYLTSFFYGLYVMYDQECVWQTEKCFSNYPEDHVLSQ Contract of the Contract of th

ŀ	HP	Q-YWYYMIELSFYWSLLFSIASDVKRKDFKEQIIHHVATIILISFSWFANYIRAGTLIMA
		. *. **. **. ** **** * . ***. *. **. *.
i	HR	KIYYYYLIELAFYSATTLTQFFDVKRKDFWEMFIHHIVTIILLCGSYTLNYTKMGAFILV
5 i	HP	LHDSSDYLLESAKMFNYAGWKNTCNNIFIVFAIVFIITRLVILPFWILHCTLVYPLELYP
		.***.** *** * ** * ******
· I	HR	VHDSADFYIEFAKMGKYANNSLVTNVGFISFTISFFLSRLVILPLWIVPSIWFYGIYTYN
ŀ	HP	AFFGYYFFNSMMGVLQLLHIFWAYLILRMAHKFITGKLVEDERSDREETESSEGEEAAAG
10		
ŀ	HR	CAMA-WLFCALL-ILQLLHFYWFSHIVKAAYASILVGVIERDTRSESEDSSAEDETAKYS
· •	HP	GGAKSRPLANGHPILNNNHRKND
		*.
15 H	HR	VGSGDYTESNGIHKRVVTAR

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T27334) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03499> (SEQ ID NOS: 5, 15 and 25)

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Determination of the whole base sequence of the cDNA insert of clone HP03499 obtained from cDNA library of human kidney revealed the structure consisting of a 129-bp 5'-untranslated region, a 1758-bp ORF, and a 86-bp 3'untranslated region. The ORF encodes a protein consisting of 585 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 5 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In translation resulted in formation of a translation product of 63 kDa that was almost identical with the molecular weight of 63,987 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 82 kDa. In addition, there exist in the amino acid sequence of this protein five sites at which N-glycosylation may occur (Asn-Ile-Thr at position 89, Asn-Glu-Thr at position 106, Asn-Ala-Thr at position 189, Asn-Arg-Thr at position 220 and Asn-Ala-Thr at position 315).

The search of the protein database using the amino 20 acid sequence of the present protein revealed that the protein was similar to Chinese hamster hypothetical protein A30227). Table 7 shows 2BE2121 (Accession No. comparison between amino acid sequences of the human protein of the present invention (HP) and Chinese hamster 25 hypothetical protein 2BE2121 (CH). Therein, the marks of -,

	*, and . represent a gap, an amino acid residue ide	entical
	with that of the protein of the present invention,	and an
	amino acid residue similar to that of the protein	of the
-	present invention, respectively. The both proteins sh	ared a
· 5	homology of 44.8% in the entire region.	÷
	Table 7	
•		
•	HP MVCREQLSKNQVKWVFAGITCVSVVVIAAIVLAITLRRPGCELEACSPDADMLDYLLSLG	
10	. ***. *.	MA TING Consideration
	CH SWSENILDYFLRNS	<u></u>
		·· •
	HP QISRRDALEVTWYHAANSKKAMTAALNSNITVLEADVNVEGLGTANETGVPIMAHPPTIY	
	. *. **** *. * . **. *	
15	CH QITTEDGAEIIWYHAANHKSQMQEALRSAAHMIEADVLLPSDGSEHGQPIMAHPPEMN	£
	HP SDNTLEQWLDAVLGSSQKGIKLDFKNIKAVGPSLDLLRQLTEEGKVRRPIWINADILKGP	
	*****. **. * . * . ******** . *	
,	CH SDNTLQEWLAEVM-KSNKGIKLDFKSLAAARASMLFLDNVKQHLQCPVWMNADVLPGP	
20		u J
	HP NMLISTEVNATQFLALVQEKYPKATLSPGWTTFYMSTSPNRTYTQAMVEKMHELVGGVPQ	
	* * * * * * * * * * * * * * * * * * * *	
	CH NG-SSKVVDAKAFLDTVTSFFPDVTFSLGWTTGWHPEKVNEGYSWTMVKEMDYICSGLTQ	
. 25	HP RVTFPVRSSMVRAAWPHFSWLLSQSERYSLTLWQAASDPMSVEDLLYVRDNTAVHQVYYD	d∑.

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HP IFEPLLSQFKQLALNATRKPMYYTGGSLIPLLQLPGDDGLNVEWLVPDVQGSGKTATMTL

5 *.** .***

CH ILEPQSHEFKQAIGI

Furthermore, the search of the GenBank using the

base sequences of the present cDNA has revealed the
registration of sequences that shared a homology of 90% or
more (for example, Accession No. R92398) among ESTs. However,
since they are partial sequences, it can not be judged
whether or not they encode the same protein as the protein
of the present invention.

<HP03500> (SEQ ID NOS: 6, 16 and 26)

Determination of the whole base sequence of the cDNA insert of clone HP03500 obtained from cDNA library of human kidney revealed the structure consisting of a 134-bp 5'-untranslated region, a 996-bp ORF, and a 476-bp 3'-untranslated region. The ORF encodes a protein consisting of 331 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 6 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro

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translation resulted in formation of a translation product of 38 kDa that was almost identical with the molecular weight of 37,694 predicted from the ORF.

The search of the protein database using the amino acid sequence of the present protein revealed that the amino acid sequence of the protein matched with that of human hypothetical protein (Accession No. AAC05803) in which a region of 62 amino acid residues from glycine at position 88 to lysine at position 149 was deleted.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA340631) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10691> (SEQ ID NOS: 7, 17 and 27)

Determination of the whole base sequence of the cDNA insert of clone HP10691 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 246-bp 5'-untranslated region, a 1038-bp ORF, and a 1096-bp 3'-untranslated region. The ORF encodes a protein consisting of 345 amino acid residues and there existed at least two putative transmembrane domains. Figure, 7 depicts the hydrophobicity/hydrophilicity profile, obtained by the

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Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human BB1 protein (Accession No. AAB37433). Table 8 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human BB1 protein (BB). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The C-terminal region of 215 amino acid residues of the present protein shared a homology of 81.9% with the N-terminal region of human BB1 protein.

Table 8

HP MSPEEWTYLVVLLISIPIGFLFKKAGPGLKRWGAAAVGLGLTLFTCGPHTLHSLVTILGT

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HP WALIQAQPCSCHALALAWTFSYLLFFRALSLLGLPTPTPFTNAVQLLLTLKLVSLASEVQ

HP DLHLAQRKEMASGFSKGPTLGLLPDVPSLMETLSYSYCYVGIMTGPFFRYRTYLDWLEQP

125 BB 1411 MASGFSKGPTLGLLRRALPDGDT-QLQLLLRGNHDRPVLPLPHLPGLAGAA 45

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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W48653) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10703> (SEQ ID NOS: 8, 18 and 28)

Determination of the whole base sequence of the cDNA insert of clone HP10703 obtained from cDNA library of human kidney revealed the structure consisting of a 359-bp

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5'-untranslated region, a 270-bp ORF, and a 1388-bp 3'untranslated region. The ORF encodes a protein consisting of 89 amino acid residues and there existed one putative domain. Figure 8 depicts transmembrane hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product of 18 kDa that was larger than the molecular weight of 10,469 predicted from the ORF.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T08343) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10711> (SEQ ID NOS: 9, 19 and 29)

Determination of the whole base sequence of the cDNA insert of clone HP10711 obtained from cDNA library of human kidney revealed the structure consisting of a 29-bp 5'-untranslated region, a 1221-bp ORF, and a 356-bp 3'-untranslated region. The ORF encodes a protein consisting of 406 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain at the N-terminus. Figure 9 depicts the

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hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 44 kDa that was almost identical with the molecular weight of 43,836 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 58 kDa. In addition, there exist in the amino acid sequence of this protein seven sites at which N-glycosylation may occur (Asn-Ser-Thr at position 65, Asn-Trp-Ser at position 95, Asn-Val-Ser at position 134, Asn-Ile-Thr at position 159, Asn-Gly-Ser at position 187, Asn-Arg-Ser at position 230 and Asn-Leu-Thr at position 333). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from glutamic acid at position 36.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to mouse kidney predominant protein (Accession No. BAA92527): Table 9 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and mouse kidney predominant protein (MM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The

both proteins shared a homology of 79.9% in the entire region.

Table 9

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HS QASPLHPALAYSLPQSPIVRAFFGSQNNFCAFNLTFGASTGPGYWDQHYLSWSMLLGVGF MM QASTLHSTLASSLPHSPIVQAFFGSQNNFCAFNLTFGAPTGPGYWDQYYLCWSMLLGMGF

HS PPVDGLSPLVLGIMAVALGAPGLMLLGGGLVLLLHHKKYSEYQSIN 5 **** ************ **** *** *** *** MM PPVDIFSPLVLGIMAVALGAPGLMFLGGGLFLLLRHRRYSEYQSIN

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10 The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA362394) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present 15 invention.

<HP10712> (SEQ ID NOS: 10, 20 and 30)

Determination of the whole base sequence of the cDNA insert of clone HP10712 obtained from cDNA library of human kidney revealed the structure consisting of a 52-bp 5'-untranslated region, a 579-bp ORF, and a 1064-bp 3'untranslated region. The ORF encodes a protein consisting of 192 amino acid residues and there existed four putative depicts the domains. Figure 10 transmembrane

hydrophobicity/hydrophilicity profile, obtained by the Kyte-25

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Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to mouse calcium channel gamma 5 subunit (Accession No. CAB86387). Table 10 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and mouse calcium channel gamma 5 subunit (MM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 75.0% in the entire region.

Table 10

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HS HSQCKWVMGSILLLVSFVLSSGGLLGFVILLRNQVTLIGFTLMFWCEFTASFLLFLNAIS

MM RSRRKWAIGSYLLLVAFILSSGGLLTFIILLKNQINLLGFTLMFWCEFTASFLFFLNAAS

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HS GLHINSITHPWE

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MM GLHINSLTQPWDPPAGTLAYRKRGYDGTSLI

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA910339) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<+ < HP03010> (SEQ ID NOS: 31, 41 and 51)

Determination of the whole base sequence of the

CDNA insert of clone HP03010 obtained from cDNA library of

human kidney revealed the structure consisting of a 97-bp

5'-untranslated region, a 1134-bp ORF, and a 320-bp 3'
untranslated region. The ORF encodes a protein consisting of

377 amino acid residues and there existed at least eight

putative transmembrane domains. Figure 11 depicts the

hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 42 kDa that was almost identical with the molecular weight of 41,462 predicted from the ORF as well as a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to Arabidopsis thaliana hypothetical protein (Accession No. AAC34490). Table 11 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Arabidopsis thaliana hypothetical protein (AT). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 42.0% in the entire region other than the N-terminal region.

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Table 11

HP MDSALSDPHNGSAEAGGPTNSTTRPPSTPEGIALAYGSLLLMALLPIFFGALRSVRCARG

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25 AT MKNCERFANLALAGLTLAPLVVRVNPNLNVILTACITVYVGCFRS

	HP KNASDMPETITSRDAARFPIIASCTLLGLYLFFKIFSQEYINLLLSMYFFVLGILALSHT
	* * * * * * * * * * * * * * * *
	AT VKDTPPTETMSKEHAMRFPLVGSAMLLSLFLLFKFLSKDLVNAVLTAYFFVLGIVALSAT
5	
	HP ISPFMNKFFPASFPNRQYQLLFTQGSGENKEEIINYEFDTKDLVCLGLSSIVGVWYLLRK
	. * *
	AT LLPAIRRFLPNPWNDNLIVWRFPYFKSLEVEFTKSQVVAGIPGTFFCAWYAWKK
10	HP HWIANNLFGLAFSLNGVELLHLNNVSTGCILLGGLFIYDVFWVFGTNVMVTVAKSFEAPI
	. * **. * *
	AT HWLANNILGLSFC1QGIEMLSLGSFKTGAILLAGLFFYDIFWVFFTPVMVSVAKSFDAPI
	HP KLVFPQDLLEKGLEANNFAMLGLGDVVIPGIFIALLLRFDISLKKNTHTYFYTSFAAYIF
15	**. **
	AT KLLFPTGDALRPYSMLGLGDIVIPGIFVALALRFDVSRRRQPQ-YFTSAFIGYAV
	en e
	HP GLGLTIFIMHIFKHAQPALLYLVPACIGFPVLVALAKGEVTEMFSYEESNPKDPAAVTES
	*. *** .*. *. ******* ***
20	AT GVILTIVVMNWFQAAQPALLYIVPAVIGFLASHCIWNGDIKPLLAFDESKTEE-ATTDES
	· · · · · · · · · · · · · · · · · · ·
	HP KEGTEASASKGLEKKEK
	the **. The Mark the control of
٠	`AT KTSEEVNKAHDE
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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA380429) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03576> (SEQ ID NOS: 32, 42 and 52)

Determination of the whole base sequence of the 10 cDNA insert of clone HP03576 obtained from cDNA library of human kidney revealed the structure consisting of a 88-bp 5'-untranslated region, a 246-bp ORF, and a 1379-bp 3'untranslated region. The ORF encodes a protein consisting of amino acid residues and there existed two putative 15 depicts the domains. 12 Figure transmembrane hydrophobicity/hydrophilicity profile, obtained by the Kytethe present protein. In Doolittle method, of translation resulted in formation of a translation product of 20 kDa that was larger than the molecular weight of 9,178 20 predicted from the ORF.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human vacuolar proton ATPase 9 kDa (Accession No. NP_003936). Table 12 shows the comparison

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between amino acid sequences of the human protein of the present invention (HP) and human vacuolar proton ATPase 9 kDa (VP). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 71.2% in the entire region.

10 Table 12

HP MTAHSFALPVIIFTTFWGLVGIAGPWFVPKGPNRGVIITMLVATAVCCYLFWLIAILAQL

VP MAYHGLTVPLIVMSVFWGFVGFLVPWFIPKGPNRGVIITMLVTCSVCCYLFWLIAILAQL :

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HP NPLFGPQLKNETIWYVRFLWE

VP NPLFGPQLKNETIWYLKYHWP

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W22566) among ESTs. However, since they are partial sequences, it can not be judged

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whether or not they encode the same protein as the protein of the present invention.

<HP03611> (SEQ ID NOS: 33, 43 and 53)

Determination of the whole base sequence of the cDNA insert of clone HP03611 obtained from cDNA library of human kidney revealed the structure consisting of a 189-bp 5'-untranslated region, a 1464-bp ORF, and a 105-bp 3'untranslated region. The ORF encodes a protein consisting of 487 amino acid residues and there existed eleven putative the 13 depicts Figure domains. transmembrane hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human cystine/glutamate transporter (Accession No. BAA82628). Table 13 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human cystine/glutamate transporter (CG). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology

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of 43.8% in the entire region other than the N-terminal region.

Table 13

-		:
HF	MGDTGLRKRREDEKSIQSQEPKTTSLQKELGLISGISIIVGTIIGS	
	.*******	
CC	MVRKPVVSTISKGGYLQGNVNGRLPSLGNKEPPGQEKVQLKRKVTLLRGVSIIIGTIIGA	
HF	GIFVSPKSVLSNTEAVGPCLIIWAACGVLATLGALCFAELGTMITKSGGEYPYLMEAYGP	Ŧ
	. ***. ** ** ** . * * **** **** *. ****. *.	7
CC	G GIFISPKGVLQNTGSVGMSLTIWTVCGVLSLFGALSYAELGTTIKKSGGHYTYILEVFGP	
HF	P IPAYLFSWASLIVIKPTSFAIICLSFSEYVCAPFYVGCKPPQIVVKCLAAAAILFISTVN	
	.** *** **. *	tu i
CC	LPAFVRVWVELLIIRPAATAVISLAFGRYILEPFFIQCEIPELAIKLITAVGITVVMVLN	
HF	SLSVRLGSYVQNIFTAAKLVIVAIIIISGLVLLAQGNTKNFDNSFEGAQLSVGAISLAFY	
	*.***	
CG	S SMSVSWSARIQIFLTFCKLTAILIIIVPGVMQLIKGQTQNFKDAFSGRDSSITRLPLAFY	Ç.
HF	NGLWAYDGWNQLNYITEELRNPYRNLPLAIIIGIPLVTACYILMNVSYFTVMTATELLQS	
	*.,**,** '**,.***,.*** *** *.* *.* *.***	
CG	YGMYAYAGWFYLNFVTEEVENPEKTIPLAICISMAIVTIGYVLTNVAYFTTINAEELLLS	

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ŀ	IP QAVAVTFGDRVLYPASWIVPLFVAFSTIGAANGTCFTAGRLIYVAGREGHMLKVLSYISV
. •	. ****** * * **. ***. * **. *.
	CG NAVAVTFSERLLGNFSLAVPIFVALSCFGSMNGGVFAVSRLFYVASREGHLPEILSMIHV
5 i	HP RRLTPAPAIIFYGIIATIYIIPGDINSLVNYFSFAAWLFYGLTILGLIVMRFTRKELERP
	*, ** **, * * ** *** *** *** *** **
. (CG RKHTPLPAVIVLHPLTMIMLFSGDLDSLLNFLSFARWLFIGLAVAGLIYLRYKCPDMHRP
1	HP IKVPVVIPVLMTLISVFLVLAPIISKPTWEYLYCVLFILSGLLFYFLFVHYKFGWAQK
10	·***· **·*····*·* · · *·* · · · · · · ·
(CG FKVPLFIPALFSFTCLFMVALSLYSDP-FSTGIGFVITLTGVPAYYLFIIWDKKPRWFRI
	HP ISKPITMHLQMLMEVVPPEEDPE
	.*. **. ** *** *.

CG MSEKITRTLQIILEVVPEEDKL

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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R07056) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03612> (SEQ ID NOS: 34, 44 and 54)

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Determination of the whole base sequence of the cDNA insert of clone HP03612 obtained from cDNA library of human kidney revealed the structure consisting of a 153-bp 5'-untranslated region, a 1128-bp ORF, and a 269-bp 3'untranslated region. The ORF encodes a protein consisting of 375 amino acid residues and there existed seven putative transmembrane domains. Figure 14 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 39 kDa that was somewhat larger than the molecular weight of 37,930 predicted from the ORF.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human monocarboxylate transporter (Accession No. AAC70919). Table 14 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human monocarboxylate transporter (MC). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 41.7% in the N-terminal region of 192 amino acid residues.

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Table 14

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	HP	MTPQP	AGPPDGGWG	WVVAAAA	FAINGLS	YGLLRSL	GLAFPDL	AEHFDRS	AQDTA₩
	-	. *.	*****	*. * *.	* *.*	*	*	. *	**
5	МС МРРМ	PSAPPVI	HPPPDGGWG	WIVVGAT	FISIGFS	SYAFPKAV	TVFFKE10	QQIFHTT	YSEIAW
	HP ISAL		4ASPVGSAL						
	MC ISSI		AGGPVSSVL						
10									
			ALGTLSRYF				LAPALQL	LLDTFGW	RGALLL
	.	**	****	*.*.*	* *** *	* .	*** *	****	. * *.
	MC GLGI	AFNLQP.	ALTIIGKYF	YRKRPMA	NGLAMAG	SNPVFLSS	LAPFNQY	LFNTFGW	KGSFLI
15	HP LGA	TLHLTP	CGALLLPLV	LPGDPP#	APPRSPLA	ALGLSLF	TRRAFSI	FALGTAL	VGGGYF
	**	*.	*.*. **	,			-	•	·
	MC·LGSI	LLNACV	AGSLMRPLO	PNQTTSI	KSKNKTGK	KTEDDSSP	KKIKTKK	STWEKVN	KYLDFS
	HP VPY	/HLAPRF	RPGPGGIRS	SAGGGR	GCDGGCGF	RPAGLRVA	GRPRLGA	PPAAAGF	RIRGSDW
20	. •		-	:			• •	:	
	MC LFKI	HRGFLIY	LSGNVIMF	.GFFAPI	IFPAPYA	KDQGIDEY	SAAFLLS	VMAFVD!	IFARPSV
-				÷.		•			
	HP AGA	VGGGAGA	RGGRRRELO	GSPAGR	GCGLWAEI	RGELRPAC	FRCTPRA	GGRRRCC	GAGHRAG
	i szint t		; ·						
25	MC CLI	ANCKALD	DDIAVEECI	EA TMENC	עראז ו רסו	I AODVTSI	VI VAVEE	CI CECS	/SSVI FF -

HP DDADEPRGAPGPSPVRLPKG

MC TLMDLVGAPRFSSAVGLVTIVECGPVLLGPPLAGKLVDLTGEYKYMYMSCGAIVVAASVW

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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI742291) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10407> (SEQ ID NOS: 35, 45 and 55)

Determination of the whole base sequence of the cDNA insert of clone HP10407 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 100-bp 5'-untranslated region, a 1053-bp ORF, and a 332-bp 3'-untranslated region. The ORF encodes a protein consisting of 350 amino acid residues and there existed at least four putative transmembrane domains. Figure 15 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the protein database using the amino acid sequence of the present protein revealed that the

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protein was longer by 35 amino acid residues at the N-terminus than human hypothetical protein (Accession No. CAB43375).

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of a clone beginning from the 117th base of the present cDNA (Accession No. AL050274).

<HP10713> (SEQ ID NOS: 36, 46 and 56)

Determination of the whole base sequence of the cDNA insert of clone HP10713 obtained from cDNA library of human kidney revealed the structure consisting of a 79-bp 5'-untranslated region, a 2004-bp ORF, and a 611-bp 3'untranslated region. The ORF encodes a protein consisting of 667 amino acid residues and there existed nine putative domains. Figure 16 transmembrane depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of present protein. the In translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to mouse retinoic acid-responsive protein (Accession No. AAC16016). Table 15 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and mouse retinoic acid-

responsive protein (MM). Therein, the marks of -, *, and represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 74.1% in the entire region.

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Table 15

MM MESQASENGSQTSSGVTDDYS--SWYIEEPLGAEEVQPEGVIPLCQLTAPPALLHACLAS

MM LSFLVLLLLALLVRRRRLWPRCGHRGLGLPSPVDFLAGDLSWTVPAAVFVVLFSNLCLLL

MM PDENPLPFLNLTAASSPDGEMETSRGPWKLLALLYYPALYYPLAACASAGHQAAFLLGTV

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		HP SKGLQSSYSEEYLRNLLCRKKLGSSYH-TSKHGFLSWARVCLRHCIYTPQPGFHLPLKLV
		* *** *** *** *** *** * * . * . **
		MM SQGLQTSYSEKYLRTLLCPKKLDSCSHPASKRSLLSRAWAFSHHSIYTPQPGFRLPLKLV
	5	HP LSATLTGTAIYQVALLLLVGVVPTIQKVRAGVTTDVSYLLAGFGIVLSEDKQEVVELVKH
		· ******* ******* ***** ***** · ****** · ******
		MM ISATLTGTATYQVALLLLVSVVPTVQKVRAGINTDVSYLLAGFGIVLSEDRQEVVELVKH
		HP HLWALEVCYISALVLSCLLTFLVLMRSLVTHRTNLRALHRGAALDLSPLHRSPHPSRQAI
	10	****.******* ***.*.**.**.*********
		MM HLWTVEACYISALVLSCASTFLLLIRSLRTHRANLQALHRGAALDLDPPLQSIHPSRQAI
•		
		HP FCWMSFSAYQTAFICLGLLVQQIIFFLGTTALAFLVLMPVLHGRNLLLFRSLESSWPFWL
		, ****, ***** ******, ******, *****, . *, *******, *****, *****
	15	MM VSWMSFCAYQTAFSCLGLLVQQVIFFLGTTSLAFLVFVPLLHGRNLLLLRSLESTWPFWL
		HP TLALAVILQNMAAHWVFLETHDGHPQLTNRRVLYAATFLLFPLNVLVGAMVATWRVLLSA
		*. *******. **. **. **. *. *. *****. *.
	•	MM TVALAVILQNIAANWIFLRTHHGYPELTNRRMLCVATFLLFPINMLVGAIMAVWRVLISS
	20	
		HP LYNAIHLGQMDLSLLPPRAATLDPGYYTYRNFLKIEVSQSHPAMTAFCSLLLQAQSLLPR

		MM LYNTVHLGQMDLSLLPQRAASLDPGYHTYQNFLRIEASQSHPGVIAFCALLLHAPSPQPR
. :	25	HP TMAAPQDSLRPGEEDEGMQLLQTKDSMAKGARPGASRGRARWGLAYTLLHNPTLQVFRKT

MM PPLAPQDSLRPAEEEEGMQLLQTKDLMAKGAGHKGSQSRARWGLAYTLLHNPSLQAFRKA

HP ALLGANGAQP

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MM ALTSAKANGTQP

of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI760170) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10714> (SEQ ID NOS: 37, 47 and 57)

Determination of the whole base sequence of the cDNA insert of clone HP10714 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 82-bp 5'-untranslated region, a 1395-bp ORF, and a 1820-bp 3'-untranslated region. The ORF encodes a protein consisting of 464 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 17 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In

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vitro translation resulted in formation of a translation product of 49 kDa that was somewhat smaller than the molecular weight of 52,340 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 52 kDa. In addition, there exist in the amino acid sequence of this protein two sites at which N-glycosylation may occur (Asn-Ala-Thr at position 164 and Asn-Asp-Ser at position 320). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from threonine at position 22.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA861134) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10716> (SEQ ID NOS: 38, 48 and 58)

Determination of the whole base sequence of the cDNA insert of clone HP10716 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 60-bp 5'-untranslated region, a 1413-bp ORF, and a 653-bp 3'-untranslated region. The ORF encodes a protein consisting of 470 amino acid residues and there existed one

putative transmembrane domain at the N-terminus. Figure 18 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 61 kDa that was larger than the molecular weight of 52,086 predicted from the ORF.

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The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human hypothetical protein CGI-90 (Accession No. AAD34085). Table 16 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human hypothetical protein CGI-90 (CG). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 32.4% in the entire region.

20 Table 16

The second of th

HP- MSRLGALGGARAGLGLLLGTAAGLGFLCLLYSQRWKRTQRHGRSQSLPNSLDYTQTSDPG

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HP RHVMLLRAVPGGAGDASVLPSLPREGQEKVLDRLDFVLTSLVALRREVEELRSSLRGLAG

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	HP EIVGEVRCHMEENQRVARRRRFPFVRERSDSTGSSSVYFTASSGATFTDAESEGGYTTAN
	CG MALAARLWRLLPFRRGAAPGSRLPA
5	HP AESDNERDSDKESEDGEDEVSCETVKMGRKDSLDLEEEAASGASSALEAGGSSGLEDVLP
	.**
	CG GPSGSRGIAAPARFRGFEVMGNPGTFNRGLLLSALSYLGFETYQVISQAAVVHATAKVEE
	HP LLQQADELHRGDEQGKREGFQLLLNNKLVYGSRQDFLWRLARAYSDMCELT-EEVSEKKS
10	.*.*** ** .* .*** .******* .*****
	CG ILEQADYLYESGETEKLYQLLTQYKESEDAELLWRLARASRDVAQLSRTSEEEKKL
•	HP YALDGKEEAEAALEKGDESADCHLWYAVLCGQLAEHESIQRRIQSGFSFKEHVDKAIALQ
	* *. ***** * ****.*. *.
15	CG LVYEALEYAKRALEKNESSFASHKWYAICLSDVGDYEGIKAKIANAYIIKEHFEKAIELN
	en de de la companya
	HP PENPMAHFLLGRWCYQVSHLSWLEKKTATALLESPLSATVEDALQSFLKAEELQPGFSKA
	* *.* ***** ** *.* *.** * .***.*
	CG PKDATSIHLMGIWCYTFAEMPWYQRRIAKMLFATPPSSTYEKALGYFHRAEQVDPNFYSK
20	
	HP GRVYISKCYRELGKNSEARWWMKLALELPDVTKEDLAIQKDLEELEVILRD
	· · · · · · · · · · · · · · · · · · ·
	CG NLLLLGKTYLKLHNKKLAAFWLMKAKDYPAHTEEDKQIQTEAAQLLTSFSEKN
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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA852295) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10717> (SEQ ID NOS: 39, 49 and 59)

Determination of the whole base sequence of the cDNA insert of clone HP10717 obtained from cDNA library of human kidney revealed the structure consisting of a 73-bp 5'-untranslated region, a 732-bp ORF, and a 976-bp 3'-untranslated region. The ORF encodes a protein consisting of 243 amino acid residues and there existed two putative transmembrane domains. Figure 19 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 36 kDa that was larger than the molecular weight of 26,270 predicted from the ORF.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI478174) among ESTs. However, since they are partial sequences, it can not be judged whether or not they

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encode the same protein as the protein of the present invention.

<HP10718> (SEQ ID NOS: 40, 50 and 60)

Determination of the whole base sequence of the cDNA insert of clone HP10718 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 86-bp 5'-untranslated region, a 813-bp ORF, and a 889bp 3'-untranslated region. The ORF encodes a protein consisting of 270 amino acid residues and there existed three putative transmembrane domains. Figure 20 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product of 28 kDa that was smaller than the molecular weight of 31,116 predicted from the ORF.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to Caenorhabditis elegans hypothetical protein Y53C10A (Accession No. CAA22139). Table 17 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Caenorhabditis elegans hypothetical protein Y53ClOA (CE). Therein, the marks of -, . *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an 25 amino acid residue similar to that of the protein of the · 5

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present invention, respectively. The both proteins sha	
homology of 54.8% in the entire region other than t	he N-
terminal region.	
Table 17	
HP MAGAEDWPGQ	
CE MTSSSAASSSTTTSSTMMPDENECLKKEEERFKSPDPAPTLDEEVDIDTLPSMLEDDPNG	• *
	* **
HP QLELDEDEASCCRWGAQHAGARELAALYSPGKRLQEWCSVILCFSLIAHNLVHLLLLARW	
, **, . ** . **** *	
CE NVVECDLGFKGPRWGPQHAGAKKLASMYSKEKRLQEKVSLFAAIFLFSIVFIN-LLLS-W	
	.2
HP EDTPLVILGVVAGALIADFLSGLVHWGADTWGSVELPIVGKAFIRPFREHHIDPTAIT	;

CE ESSIWVSVLVSAVLGIMTADFASGLVHWAADTFGSVE-TWFGRSFIRPFREHHVDPTAIT	
HP RHDFIETNGDNCLVTLLPLLNMAYKFRTHSPEALEQLYPWECFVFCLIIFGTFTNQIH	
*** * ***** * *** * . * * * * * * * * * * * * * * * * * *	2
CE RHDIVEVNGDNCMLCVGPLLWILYQQMTYQRDAITQWATFHWYILLLGIYVALTNQIH	
and the second of the second o	
HP KWSHTYFGLPRWYTLLQDWHYILPRKHHRIHHVSPHETYFCITTGWLNYPLEKIGFWRRL	

CE KWSHTYFGLPTWVVFLQKAHIILPRSHHKIHHISPHACYYCITTGWLNWPLEYIGFWRKM

HP EDLIQGLTGEKPRADDMKWAQKIK

* .. . ** . **. **. *** *.

CE EWVVTTVTGMQPREDDLKWATKLQ

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or 10 (for example, Accession No. AA176107) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention. In addition, the region from position 466 to position 778 of the cDNA of the present 15 invention matched with the region from position 2 of human ubiquitin-conjugating enzyme position 314 variant 1 (Accession NO. NM 003349) although no match was observed in another region.

<HP03745> (SEQ ID NOS: 61, 71 and 81)

Determination of the whole base sequence of the cDNA insert of clone HP03745 obtained from cDNA library of human kidney revealed the structure consisting of a 99-bp 5'-untranslated region, a 1170-bp ORF, and a 107-bp 3'-untranslated region. The ORF encodes a protein consisting of 389 amino acid residues and there existed at least nine

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putative transmembrane domains. Figure 21 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human solute carrier family 7 (Accession No. NP_003974). Table 18 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human solute carrier family 7 (SC). Therein, the marks of -, *, and represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 36.0% in the N-terminal region of 397 amino acid residues.

Table 18

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MDRGEKIQLKRVFGYWWGTSFLLINIIG

.*.***... *.*.*

SC MEAREPGRPTPTYHLVPNTSQSQVEEDVSSPPQRSSETMQLKKEISLLNGVSLVVGNMIG

25 HP-AGIFVSPKGVLAYSCMNVGVSLCVWAGCAILAMTSTLCSAEISISFPCSGAQYYFLKRYF as

			******	. * ** ***	** **	k *	** *	*
		SC S	SGIFVSPKGVLYHT-	ASYGMSLIVWAIGG	LFSVVGALCYAE	ELGTTITKS	GASYAYILI	EAF
		HP G	GSTVAFLNLWTSLFL	.GSGVVAG-QALLLA	EYSIQPFFPSCS	SVPKLPKKO	CLALAMLWI	VGI
	5	*	· ** **. ** _. .	**.	* *** ****.	* *	** *	
		SC G	GGFIAFIRLWVSLLV	VEPTGQAIIAITFAI	NYIIQPSFPSCD	PPYLACRL	LAAACICLI	LTF
		HP L	.TSRGVKEVTWLQIA	SSVLKVSILSFISL	rgvvflirgkke	NVERFQNA	FDAELPDIS	SHL
			** ** .	. ** * * .	*.* * .*	. *.**.*	* *	.*
	10	SC V	NCAYVKWGTRVQDT	FTYAKVVALIAIIV	MGLVKLCQG	HSEHFQDA	FEGSSWDMO	GNL
				•				
•		HP I	QAIFQGYFAYSG	ELKKPRT	FIPKCIFTALPL	.VTVVYLLV	NISYLTVL	rPR
		t	*.:	*,*,*	.* **.	** *. *.	* * ***.	•
		SC S	SLALYSALFSYSGWD	TLNFVTEEIKNPER	NLPLAIGISMPI	VTLIYILT	NVAYYTVLI	VIS
	15	•					•	
•		HP E	EILSSDAVAITWADR	AFPSLAWIMPFAIS1	rslfsnllisif	KSSRPIYL	ASQEGQLPI	LF
		* 27 %	`,*******,*.**.	.***.	* ** ***	***	. *. **. **	*.
		SC D	VLSSDAVAVTFADQ	TFGMFSWTIPIAVAL	LSCFGGLNASIF	ASSRLFFV	GSREGHLPI	DLL
				•				
	20	HP N	TLNSHS-SPFTAVL	LLVTLGSLAIILTSI	LIDLINYIFFTG	SLWSILLM	IGILRRRYG	QEP
		•.••	**.*	*	****. *.	*.	.** *	**
		SC S	SMIHIERFTPIPALL	FNCTMALIYLIVED	/FQLINYFSFSY	WFFVGLSV	VGQLYLRWI	ŒP
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SC KRPRPLKLSVFFPIVFCICSVFLVIVPLFTDTINSLIGIGIALSGVPFYFMGVYLPESRR

<HP03747> (SEQ ID NOS: 62, 72 and 82)

Determination of the whole base sequence of the cDNA insert of clone HP03747 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 21-bp 5'-untranslated region, a 1047-bp ORF, and a 1324-bp 3'-untranslated region. The ORF encodes a protein consisting of 348 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain at the C-terminus. Figure 22 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 40 kDa that was almost identical with the molecular weight of 39,685 predicted from the ORF. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from proline at position 39.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human endoplasmic reticulum glycoprotein (Accession No. NP_006807). Table 19 shows the comparison between amino acid sequences of the human protein

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of the present invention (HP) and human endoplasmic reticulum glycoprotein (ER). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 54.1% in the entire region.

Table 19

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ER REHSLIKPYQGVGSSSMPLWDFQGSTMLTSQYVRLTPDERSKEGSIWNHQPCFLKDWEMH

- HP VHFKIHGQGKKNLHGDGLAIWYTKDRMQPGPVFGNMDKFVGLGVFVDTYPNEEKQQERVF

 ****. ** *********. *. ******. *. * **. * *****

 ER VHFKVHGTGKKNLHGDGIALWYTRDRLVPGPVFGSKDNFHGLAIFLDTYPNDET-TERVF
- ER PYISVMVNNGSLSYDHSKDGRWTELAGCTADFRNRDHDTFLAVRYSRGRLTVMTDLEDKN ...

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA262924) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10719> (SEQ ID NOS: 63, 73 and 83)

Determination of the whole base sequence of the cDNA insert of clone HP10719 obtained from cDNA library of human kidney revealed the structure consisting of a 54-bp

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5'-untranslated region, a 786-bp ORF, and a 576-bp 3'-untranslated region. The ORF encodes a protein consisting of 261 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the inner portion. Figure 23 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 33 kDa that was larger than the molecular weight of 27,435 predicted from the ORF. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from asparagine at position 19.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to mouse endomucin (Accession No. AAD05208). Table 20 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and mouse endomucin (MM). Therein, the marks of -, *, and represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 47.9% in the entire region.

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MM	SVKLLTVKTISHESGEHSAQGKTKN

HР	SVKLLTVKTISHESGEHSAQGKTKN
MM	KIATTPSTTPSYSSIILPVVIALVVITLLVFTLVGLYRICWKRDPGTPENGNDQPQSDKE
-	* * * , * , * , ************ ** ** ** **
НР	KNASTSATSRSYSSIILPVVIALIVITLSVFVLVGLYRMCWKADPGTPENGNDQPQSDKE
MM	STLPGSQNKITTQLLDALPKITATPSASLTTAHTMSLLQDTEDR
	***. *. **
ΗР	STLQSSKPKTETQSSIKTTEIPGSVLQPDASPSKTGTLTSIPVTIPENTSQSQVIGTEGG
MM	DRILLERITUODA 2612FATTIN2FILLIGIFAQ111FQL FIGURO219971111111111111111111111111111111111
101	.**. *. ** **
HP	TGTTPKGTITNELLKMSLMSTATFLTSKDEGLKATTTDVRKNDSIISNVTVTSVTLPNAV
	The second of th
MM	MRLLQATVLFFLLSNSLCHSEDGKDVQNDSIPTPAETSTTKASVTIPGIVSV-TNPNKPA
	* ***, *, * ***, *, * *,
	MELLQVTIL-FLLP-SIC-SSNSTGVL-EAANNSLVVTTTKPSITTPNTESLQKNVVTPT

sequences that shared a homology of 90% or more (for example, Accession No. AA486620) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10720> (SEQ ID NOS: 64, 74 and 84)

Determination of the whole base sequence of the cDNA insert of clone HP10720 obtained from cDNA library of human kidney revealed the structure consisting of a 25-bp 10 5'-untranslated region, a 669-bp ORF, and a 653-bp 3'untranslated region. The ORF encodes a protein consisting of 222 amino acid residues and there existed a putative secretory signal at the N-terminus and one transmembrane domain in the inner portion. Figure 24 depicts 15. the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 28 kDa that was somewhat larger than the molecular weight of 25,219 predicted from the ORF. In this case, the addition 20 of a microsome led to the formation of a product of 35 kDa. In addition, there exist in the amino acid sequence of this protein two sites at which N-glycosylation may occur (Asn-Val-Thr at position 76 and Asn-His-Thr at position 93). Application of the (-3,-1) rule, a method for predicting the 2.5 cleavage site of the secretory signal sequence, allows to

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expect that the mature protein starts from glutamic acid at position 15.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI792241) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

10 <HP10721> (SEQ ID NOS: 65, 75 and 85)

Determination of the whole base sequence of, the cDNA insert of clone HP10721 obtained from cDNA library of human kidney revealed the structure consisting of a 74-bp 5'-untranslated region, a 552-bp ORF, and a 1658-bp 3'-untranslated region. The ORF encodes a protein consisting of 183 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the inner portion. Figure 25 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 23 kDa that was somewhat larger than the molecular weight of 19,989 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 22 kDa. Application of the (-3,-1) rule, a method for predicting the

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cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from glutamic acid at position 25.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R27187) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10725> (SEQ ID NOS: 66, 76 and 86)

Determination of the whole base sequence of the cDNA insert of clone HP10725 obtained from cDNA library of human kidney revealed the structure consisting of a 235-bp 5'-untranslated region, a 789-bp ORF, and a 713-bp 3'-untranslated region. The ORF encodes a protein consisting of 262 amino acid residues and there existed one putative transmembrane domain. Figure 26 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example,

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Accession No. AI127782) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10727> (SEQ ID NOS: 67, 77 and 87)

Determination of the whole base sequence of the cDNA insert of clone HP10727 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 102-bp 5'-untranslated region, a 507-bp ORF, and a 947bp 3'-untranslated region. The ORF encodes a protein consisting of 168 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the inner portion. Figure 27 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 24 kDa that was larger than the molecular weight of 17,822 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 23 kDa. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from lysine at position 29.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of

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sequences that shared a homology of 90% or more (for example, Accession No. R80316) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

- <HP10728> (SEQ ID NOS: 68, 78 and 88)

Determination of the whole base sequence of the cDNA insert of clone HP10728 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 221-bp 5'-untranslated region, a 732-bp ORF, and a 902-bp 3'-untranslated region. The ORF encodes a protein consisting of 243 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 28 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 30 kDa that was larger than the molecular weight of 26,534 predicted from the ORF.

of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H23535) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP10730> (SEQ ID NOS: 69, 79 and 89)

Determination of the whole base sequence of the cDNA insert of clone HP10730 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 27-bp 5'-untranslated region, a 1287-bp ORF, and a 1216-bp 3'-untranslated region. The ORF encodes a protein consisting of 428 amino acid residues and there existed one putative transmembrane domain. Figure 29 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 50 kDa that was somewhat larger than the molecular weight of 48,992 predicted from the ORF.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. C19105) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10742> (SEQ ID NOS: 70, 80 and 90)

Determination of the whole base sequence of the cDNA insert of clone HP10742 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 231-bp 5'-untranslated region, a 852-bp ORF, and a 828-

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bp 3'-untranslated region. The ORF encodes a protein consisting of 283 amino acid residues and there existed two putative transmembrane domains. Figure 30 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 30 kDa that was smaller than the molecular weight of 31,629 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T35949) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03800> (SEQ ID NOS: 91, 101 and 111)

Determination of the whole base sequence of the cDNA insert of clone HP03800 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 67-bp 5'-untranslated region, a 1431-bp ORF, and a 135-bp 3'-untranslated region. The ORF encodes a protein consisting of 476 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 31 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In

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vitro translation resulted in formation of a translation product of 55 kDa that was almost identical with the molecular weight of 54,110 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 58 kDa. In addition, there exist in the amino acid sequence of this protein four sites at which N-glycosylation may occur (Asn-Lys-Thr at position 81, Asn-Met-Thr at position 132, Asn-Val-Thr at position 307 and Asn-Gln-Thr at position 346). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from leucine at position 23.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to mosquito vitellogenic carboxypeptidase (Accession No. P42660). Table 21 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and mosquito vitellogenic carboxypeptidase (VC). Therein, the marks of -, *, and represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 44.5% in the entire region. In addition, the C-terminal portion beginning from alanine at position 182 matched with

human probable carboxypeptidase (Accession No. AAC23787) except one amino acid residue. Table 21 5 HP MVGAMWKVIVSLVLLMPGPCDGLFRSLYRSVSMPPK-GDSGQPLFLTPYIEAGKIQKG ...* * . . ** * ** ***** . . *** VC MVKFHLLVLIAFTCYTCSDATLWNPYKKLMRGSASPPRPGESGEPLFLTPLLQDGKIEEA 10 HP RELSLYGPFPGLNMKSYAGFLTVNKTYNSNLFFWFFPAQIQPEDAPVVLWLQGGPGGSSM VC RNKARVNHPMLSSVESYSGFMTVDAKHNSNLFFWYVPAKNNREQAPILVWLQGGPGASSL HP FGLFVEHGPYVVTSNMTLRDRDFPWTTTLSMLYIDNPVGTGFSFTDDTHGYAVNEDDVAR 15 VC FGMFEENGPFH1HRNKSVKQREYSWHQNHHM1Y1DNPVGTGFSFTDSDEGYSTNEEHVGE HP DLYSALIQFFQIFPEYKNNDFYVTGESYAGKYVPAIAHLIHSLNPVREVKINLNGIAIGD . * . . *** . ** . . **, . ***, **, *** . . . ** * . . . ****, * **** 20 VC NLMKFIQQFFVLFPNLLKHPFYISGESYGGKFVPAFGYAIH—NSQSQPKINLQGLAIGD HP GYSDPESIIGGYAEFLYQIGLLDEKQKKYFQKQCHECIEHIRKQNWFEAFEILDKLLDGD VC GYTDPLNQL-NYGEYLYELGLIDLNGRKKFDEDTAAAIACAERKDMNSANRLIQGLFDG-

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	HP LTSDPSYFQNVTGCSNYYNFLRC-TEPEDQLYYVKFLSLPEVRQAIHVGNQTFNDGTIVE
	* ***. *** *. **** *
	VC LDGQESYFKKVTGFSSYYNFIKGDEESKQDSVLMEFLSNPEVRKGIHVGELPFHDSDGHN
5	HP KYLREDTVQSVKPWLTEIMNNYKVLIYNGQLDIIVAAALTEHSLMGMDWKGSQEYKK
	* * **** ** * **.****** ** ** *
	VC KVAEMLSEDTLDTVAPWVSKLLSHYRVLFYNGQLDIICAYPMTVDFLMKMPFDGDSEYKR
	HP AEKKVWKIFKSDSEVAGYIRQAGDFHQVIIRGGGHILPYDQPLRAFDMINRFIYGKGWDP
10	* *. *. *. ** * * * * * * *
10	VC ANREIYRVDGEIAGYKKRAGRLQEVLIRNAGHMVPRDQPKWAFDMITSFTHKNYL
	THE THE SECOND S
	HP YVG
15	en de la companya de La companya de la co
	The search of the GenBank using the base sequence
	of the present cDNA has revealed the registration o
	sequences that shared a homology of 90% or more (for example
	Accession No. AA095665) among ESTs. However, since they ar

of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA095665) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03831> (SEQ ID NOS: 92, 102 and 112)

Determination of the whole base sequence of the con con insert of clone HP03831 obtained from cDNA library of

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human kidney revealed the structure consisting of a 191-bp 5'-untranslated region, a 681-bp ORF, and a 223-bp 3'-untranslated region. The ORF encodes a protein consisting of 226 amino acid residues and there existed four putative transmembrane domains. Figure 32 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human claudin-10 (Accession No. NP_008915). Table 22 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human claudin-10 (CD). Therein, the marks of -, *, and represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 76.2% in the entire region. The C-terminal region downstream from glycine at position 72 completely matched with that sequence.

Table 22

	HP MSRAQIWALVSGVGGFGALVAATTSNEWKVTTRASSVITATWVYQGLWMNCAGNALGS	
	. * * * ***. * ***. * *	
	CD MASTASEIIAFMVSISGWVLVSSTLPTDYWKVSTIDGTVITTATYWANLWKACVTDSTGV	•
5	HP FHCRPHFTIFKVAGYIQACRGLMIAAVSLGFFGSIFALFGMKCTKVGGSDKAKAKIACLA	
	·*. · · · · · · · · · *****************	
	CD SNCKDFPSMLALDGYIQACRGLMIAAVSLGFFGSIFALFGMKCTKVGGSDKAKAKIACLA	
	HP GIVFILSGLCSMTGCSLYANKITTEFFDPLFVEQKYELGAALFIGWAGASLCIIGGVIFC	
LO	******************	· 2;
	CD GIVFILSGLCSMTGCSLYANKITTEFFDPLFVEQKYELGAALFIGWAGASLCIIGGVIFC	7,*
	HP FSISDNNKTPRYTYNGATSVMSSRTKYHGGEDFKTTNPSKQFDKNAYV	
	***************	4
15	CD FSISDNNKTPRYTYNGATSVMSSRTKYHGGEDFKTTNPSKQFDKNAYV	:•

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. N41613) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

25... <HP03879> (SEQ ID NOS: 93, 103 and 113) __ ==

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Determination of the whole base sequence of the cDNA insert of clone HP03879 obtained from cDNA library of human kidney revealed the structure consisting of a 33-bp 5'-untranslated region, a 918-bp ORF, and a 651-bp 3'-untranslated region. The ORF encodes a protein consisting of 305 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 33 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 34 kDa that was almost identical with the molecular weight of 34,073 predicted from the ORF.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human NADH-cytochrome b5 reductase (Accession No. Y09501). Table 23 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human NADH-cytochrome reductase (CT). Therein, the marks of -, \star , and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 63.5% in the entire region other than the N-terminal region.

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Table 23

	HP	MGIQTSPVLLASLGVGLVTLLGLAVGSYLVRRSRRPQVTLLDPNEKYLLRLLDKTTVSHN
	•	* ** * * * * ** ** *** * * ***. ** **.
5	ст ст	MGAQLSTLGHMVLFPVWFLYSLLMKLFQRS-TPAITLESPDIKYPLRLIDREIISHD
	НР	TKRFRFALPTAHHTLGLPVGKHIYLSTRIDGSLVIRPYTPVTSDEDQGYVDLVIKVYLKG
		*. ****** *. ******. ****. **. **.
	СТ	TRRFRFALPSPQHILGLPVGQHIYLSARIDGNLVVRPYTPISSDDDKGFVDLVIKVYFKD
10)	
	НР	VHPKFPEGGKMSQYLDSLKVGDVVEFRGPSGLLTYTGKGHFNIQPNKKSPPEPRVAKKLG
		. *****. ******* * ** ******* * ***. * *
	СТ	THPKFPAGGKMSQYLESMQIGDTIEFRGPSGLLVYQGKGKFAIRPDKKSNPIIRTVKSVG
•		
15	5 HP	MIAGGTGITPMLQLIRAILKVPEDPTQCFLLFANQTEKDIILREDLEELQARYPNRFKLW
•		*********************************
	СТ	MIAGGTGITPMLQVIRAIMKDPDDHTVCHLLFANQTEKDILLRPELEELRNKHSARFKLW
-		
•	НР	FTLDHPPKDWAYSKGFVTADMIREHLPAPGDDVLVLLCGPPPMVQLACHPNLDKLGYSQK
2	0	, ***. , *. , *. , ***. ***. ***. **
	СТ	YTLDRAPEAWDYGQGFVNEEMIRDHLPPPEEEPLVLMCGPPPMIQYACLPNLDHVGHPTE
	· HF	MRFTY
	٠.,	
2	- C1	DCEVE

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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. F06459) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

10 <HP03880> (SEQ ID NOS: 94, 104 and 114)

Determination of the whole base sequence of the cDNA insert of clone HP03880 obtained from cDNA library of human kidney revealed the structure consisting of a 98-bp 5'-untranslated region, a 684-bp ORF, and a 115-bp 3'untranslated region. The ORF encodes a protein consisting of 227 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 34 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In translation resulted in formation of a translation product of 28 kDa that was somewhat larger than the molecular weight of 25,717 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 27 kDa. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to

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expect that the mature protein starts from aspartic acid at position 23.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to rat phosphatidylethanolamine-binding protein (Accession No. P31044). Table 24 shows the comparison between amino acid sequences of the human protein invention (HP) and rat of present the phosphatidylethanolamine-binding protein (RN). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 37.6% in the region of 133 amino acid residues other than the N-terminal region.

Table 24

HP MGWTMRLVTAALLLGLMMVVTGDEDENSPCAHEALLDEDTLFCQGLEVFYPELGNIGCKV

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RN MAADISQWAGPLSLQEVDEPPQHALRVDYGGVTV

HP VPDCNNYRQKITSWMEPIVKFPGAVDGATYILVMVDPDAPSRAEPRQRFWRHWLVTDIKG

* * *.**. ******* .*. * *.**...**

RN DELGKVLTPTQVMNRPSSISWDGLDPGKLYTLVLTDPDAPSRKDPKFREWHHFLVVNMKG

HP ADLKKGKIOGOELSAYOAPSPPAHSGFHRYOFFVYLOEGKV---ISLLP-KENKTRGSWK

RN NDISSGTV----LSEYVGSGPPKDTGLHRYVWLVYEQEQPLNCDEPILSNKSGDNRGKFK

5

HP MDRFLNRFHLGEPEASTQFMTQNYQDSPTLQAPRERASEPKHKNQAEIAAC

* . . *** * * * . . . * *.

RN VESFRKKYHLGAPVAGTCFQAEWDDSVPKLHDQLAGK

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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H83784) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10704> (SEQ ID NOS: 95, 105 and 115)

Determination of the whole base sequence of the

CDNA insert of clone HP10704 obtained from cDNA library of

human kidney revealed the structure consisting of a 141-bp

5'-untranslated region, a 1326-bp ORF, and a 399-bp 3'
untranslated region. The ORF encodes a protein consisting of

441 amino acid residues and there existed eight putative

transmembrane domains. Figure 35 depicts the

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hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human unknown gene product (Accession No. AAC27544). Table 25 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human unknown gene product (UP). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 39.1% in the entire region.

Table 25

HP MAIHKALVMCLGLPLFLFPG-AWAQGHVPPGCSQGLNPLYYNLCDRSGAWGIVLE

20 * **... * ... **. . * * * . ***. *

UN MFVASERKMRAHQVLTFLLLFVITSVASENASTSRGCGLDLLPQYVSLCDLDAIWGIVVE

25 UN AVAGAGALITLLLMLILLVRLPFIKEKEKKSPVGLHFLFLLGTLGLFGLTFAFIIQEDET (25)

HP TCASRRFLFGVLFAICFSCLAAHVFALNFLARKNHGPRGWVIFTVALLLTLVEVIINT
. *. ****. ***** *****
UN. ICSVRRFLWGVLFALCFSCLLSQAWRVRRLVRHGTGPAGWQLVGLALCLMLVQVIIAV
HP LIITLVRGSGEGGPQGNSSAGWAVASPCAIANMDFVMALIYVMLLLLGAFLGAWPALC
*** * * * .**
UN LVLTVLRDTRPACAYEPMDFVMALIYDMVLLVVTLGLALFTLC
HP YKRWRKHGVFVLLTTATSVAIWVVWIVMYTYGN-KQHNSPTWDDPTLAIALAANAWAF
. *** *. *. *. ** ***. * ** ** * *. *
UN FKRWKLNGAFLLITAFLSVLIWVAWMTMYLFGNVKLQQGDAWNDPTLAITLAASGWVF
HP FYVIPEVSQVTKSSPEQSYQGDMYPTRGVGY-ETILKEQ-KGQSMFVENKAFSMDEPV
**** * *
JN FHAIPEI-HCTLLPALQENTPNYFDTSQPRMRETAFEEDVQLPRAYMENKAFSMDEHN
HP KRPVS-PYSGYNGQLLTSVYQPTEMALMHKVPSEGAYDIILPRATANSQVMGSANSTL
* *
JN LRTAGFPNGSLGKRPSGSLGKRPSAPFRSNVYQPTEMAVVLNGGTIPTAPPSHTGRHL
The state of the s
IP EDMYSAQSHQAATPPKDGKNSQVFRNPYVWD

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of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA346702) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10715> (SEQ ID NOS: 96, 106 and 116)

Determination of the whole base sequence of the cDNA insert of clone HP10715 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 49-bp 5'-untranslated region, a 798-bp ORF, and a 1351-bp 3'-untranslated region. The ORF encodes a protein consisting of 265 amino acid residues and there existed two putative transmembrane domains. Figure 36 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 43 kDa that was larger than the molecular weight of 29,217 predicted from the ORF.

of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI381750) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present

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<HP10724> (SEQ ID NOS: 97, 107 and 117)

Determination of the whole base sequence of the cDNA insert of clone HP10724 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 68-bp 5'-untranslated region, a 627-bp ORF, and a 1485-bp 3'-untranslated region. The ORF encodes a protein consisting of 208 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 37 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 24 kDa that was almost identical with the molecular weight of 23,850 predicted from the ORF.

of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T78035) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10733> (SEQ ID NOS: 98, 108 and 118)

Determination of the whole base sequence of the cDNA insert of clone HP10733 obtained from cDNA library of human umbilical cord blood revealed the structure consisting

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of a 102-bp 5'-untranslated region, a 1203-bp ORF, and a 222-bp 3'-untranslated region. The ORF encodes a protein consisting of 400 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the inner portion. Figure 38 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 50 kDa that was larger than the molecular weight of 43,151 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 54 kDa. In addition, there exist in the amino acid sequence of this protein four sites at which N-glycosylation may occur (Asn-Leu-Thr at position 52, Asn-Ala-Ser at position 131, Asn-Ile-Thr at position 145 and Asn-Leu-Ser at position 343). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from arginine at position 33.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to Drosophila melanogaster GOLIATH protein (Accession No. Q06003). Table 26 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Drosophila melanogaster

GOLIATH protein (DM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 35.0% in the entire region.

Table 26

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HP	MAWRRREASVGARGVLALALLALALCVPGARGRALEWFSAVVNIEYVDPQTNLTVWS
HР	SGRFGDSSPKEGAHGLVGVPWAPGGDLEGCAPDTRFFVPEPGGRGAAPWVALVARGG
НР	KDKVLVAARRNASAVVLYNEERYGNITLPMSHAGTGNIVVIMISYPKGREILEL-VQ
	* **.*.*.
DM	MQLEKMQIKGKTRNIAAVITYQNIGQDLSLTLDI
HP	PVTMTIGVGTRHVQEFISGQSVVFVAIAFITMMIISLAWLIFYYIQRFLY-TGSQ
	*** * * * **.**. * * ******* *
DM	NVTISIIEGRRGVRTISSLNRTSVLFVSISFIVDDILCWLIFYYIQRFRYMQAKDO
HP	QSHRKETKKVIGQLLLHTVKHGEKGIDVDAENCAVCIENFKVKDIIRILPCKHIFHR
DM	RNLCSVTKKAIMKIPTKTGKFSD-EKDLDSDCCAICIEAYKPTDTIRILPCKHEFHKI
	and the state of t

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	HP	DPWLLDHRTCPMCKLDVIKALGYWGEPGDVQEMPAPESPPGRDPAANLSLALPDDDGSDE
	•	****, ********* **
	DM	DPWLIEHRTCPMCKLDVLKFYGY-VVGDQIYQTPSPQHTAPIASIEEVPVIVVAVPHGPQ
5	HP	SSPPSASPAESEPQCDPSFKGDAGENTALLEAGRSDSRHGGPIS
		* * *
	DM	PLQPLQASNMSSFAPSHYFQSSRSPSSSVQQQLAPLTYQPHPQQAASERGRRNSAPATMP

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI286184) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10734> (SEQ ID NOS: 99, 109 and 119)

Determination of the whole base sequence of the cDNA insert of clone HP10734 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 124-bp 5'-untranslated region, a 579-bp ORF, and a 1202-bp 3'-untranslated region. The ORF encodes a protein consisting of 192 amino acid residues and there existed one putative transmembrane domain. Figure 39 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-

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Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human sodium channel ß2 subunit (Accession No. AAD47196). Table 27 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human sodium channel ß2 subunit (SC). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 26.3% in the N-terminal region of 152 amino acid residues.

Table 27

HP DOGTYICEIRLKGESQYFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVE

SC DEGIYNCYIMNPPDRHRGHGKIHLQVLMEEPPERDFTVAVIVGASVGGFLAVVILVLMVV

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HP WIFSGRRAKVTRRKHHCVREGSG

SC KCVRRKKEQKLSTDDLKTEEEGKTDGEGNPDDGAK

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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. C03216) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10756> (SEQ ID NOS: 100, 110 and 120)

Determination of the whole base sequence of the

CDNA insert of clone HP10756 obtained from cDNA library of
human kidney revealed the structure consisting of a 49-bp
5'-untranslated region, a 783-bp ORF, and a 166-bp 3'untranslated region. The ORF encodes a protein consisting of
260 amino acid residues and there existed a putative
secretory signal at the N-terminus. Figure 40 depicts: the

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hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 27 kDa that was almost identical with the molecular weight of 27,356 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AW027769) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03670> (SEQ ID NOS: 121, 131 and 141)

Determination of the whole base sequence of the cDNA insert of clone HP03670 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 77-bp 5'-untranslated region, a 1014-bp ORF, and a 531-bp 3'-untranslated region. The ORF encodes a protein consisting of 337 amino acid residues and there existed at least seven putative transmembrane domains. Figure 41 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human hypothetical protein KIAA0260

(Accession No. BAA13390). Table 28 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human hypothetical protein KIAA0260 (KI). Therein, the marks of -, *, and represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 57.6% in the entire region other than the N-terminal region. In addition, the C-terminal region beginning from leucine at position 77 matched with human putative Sqv-7-like protein (Accession No. AJ005866) except one amino acid residue.

Table 28

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HP MTAGGQAEAEGAGGEPG

KI NSWSPLGAAAAGPRAARPRRQATAAAAAMAEVHRRQHARVKGEAPAKSSTLRDEEELGMA

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HP NKIIHFPDFDKKIPVKLFPLPLLYVGNHISGLSSTSKLSLPMFTVLRKFTIPLTLLLETI

- KI LRVVKFPDLDRNVPRKTFPLPLLYFGNQITGLFSTKKLNLPMFTVLRRFSILFTMFAEGV
- 5 KI LLKKTFSWGIKMTVFAMIIGAFVAASSDLAFDLEGYAFILINDVLTAANGAYVKQKLDSK

 - KI ELGKYGLLYYNALFMILPTLAIAYFTGDAQKAVEFEGWADTLFLLQFTLSCVMGFILMYA
 - HP TVLCSYYNSALTTAVVGAIKNVSVAYIGILIGGDYIFSLLNFVGLNICMAGGLRYSFLTL

 ****. *******..** ***...*****... **...****...**...**

 KI TVLCTQYNSALTTTIVGCIKNILITYIGMVFGGDYIFTWTNFIGLNISIAGSLVYSYITF
- 15 HP SSQLKPKPVGEENICLDLKS
 -*. * * **. *.
 - KI TEEQLSKQ-SEANNKLDIKGKGAV

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R24922) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present

invention.

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<HP03688> (SEQ ID NOS: 122, 132 and 142)

Determination of the whole base sequence of the cDNA insert of clone HP03688 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 35-bp 5'-untranslated region, a 711-bp ORF, and a 1729-bp 3'-untranslated region. The ORF encodes a protein consisting of 236 amino acid residues and there existed five putative transmembrane domains. Figure 42 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to Caenorhabditis elegans hypothetical protein W02D9 (Accession No. CAB03470). Table 29 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Caenorhabditis elegans hypothetical protein W02D9 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 50.8% in the entire region other than the N-terminal

	region.
	Table 29
. 5	НР МАЕАЕЕ
	CE MEILNLSSKFSLSDKPCQKFIFSLFSAVQNSRFKIISFPEIHQKPLPQEEMNSFGNASVD
. 10	HP SPGDPGTASPRPLFAGLSDISISQDIPVEGEITIPMRSRIREFDSSTLNESVRNTIMRDL
	CE IDMLEQEMAAEQTANLSGNIAGMSAPKSSSNRRGPMQEVDLDAEFDTLEEPVWDTVKRDV
•	HP KAVGKKFMHVLYPR-KSNTLLRDWDLWGPLILCVTLALMLQRDSADSEKDGGPQFAEVFV
15	. ** ** **. * ********** **. **
	HP IVWFGAVTITLNSKLLGGNISFFQSLCVLGYCILPLTVAMLICRLVLLADPGPVNFMVRL ***.*.* * **************** **** .*
20	CE ITFFGSVIVTANIKLLGGNISFFQSLCVIGYCLLPPFVAAVLCSL-FLHGIAFPLRL
	HP FVVIVMFAWSIVASTAFLADSQPPNRRALAVYPVFLFYFVISWMILTFTPQ *.**. ** .*** * *********.
	CE LITSIGFVWSTYASMGFLAGCQPDKKRLLVIYPVFLFYFVVSWMIISHS

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T51465) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03825> (SEQ ID NOS: 123, 133 and 143)

Determination of the whole base sequence of the cDNA insert of clone HP03825 obtained from cDNA library of human kidney revealed the structure consisting of a 20-bp 5'-untranslated region, a 1683-bp ORF, and a 36-bp 3'-untranslated region. The ORF encodes a protein consisting of 560 amino acid residues and there existed seven putative transmembrane domains. Figure 43 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 56 kDa that was smaller than the molecular weight of 64,047 predicted from the ORF.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to Mycobacterium tuberculosis hypothetical protein Rv0235c (Accession No. CAB07001). Table 30 shows the comparison between amino acid sequences

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of the human protein of the present invention (HP) and Mycobacterium tuberculosis hypothetical protein Rv0235c (MT). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 41.7% in the entire region other than the N-terminal region. In addition, the region from alanine at position 293 to proline at position 502 matched with human putative novel protein c360B4.1 (Accession No. CAB56180).

Table 30

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HF	MAAPAESLRRRKTGYSDPEPESPPAPGRGPAGSPAHLHTGTFWLTRIVLLKALAFVYFVA
	**. * * * *
MT	MGWFSAPEYWLGRLALERGTAIIYLIA
HF	P FLVAFHQNKQLIGDRGLLPCRVFLKNFQQYFQDRTSWEVFSYMPTILWLMDWSDMNSNLD
	.******
МТ	FVAAAQQFRPLIGEHGMLPVPRYLAG-QSFWRTPSIFH-FRYSDRVFAGVCWLGAVLS
HF	LLALLGLGISSFVLITGCANMLLMAALWGLYMSLVNVGHVWYSFGWESQLLETGFLGIFL
;	* . * . * * . * . * . * . * . * . * . *
МТ	AAVVAGAASFVPLWATMLIWLTLWVLYLSIVNVGQAWYSFGWESLLLETGFLMIFL

	HP CPLWTLSRLPQHTPTSRIVLWGFRWLIFRIMLGAGLIKIRGDRCWRDLTCMDFHYETQPM	,
	. * * * * * * * * * * * * * * * * * * *	
	MT GNERTAPPILTLLLA-RWLLFRVEFGAGLIKMRGDSCWRSLTCLYYHHETQPM	
5		
	HP PNPVAYYLHHSPWWFHRFETLSNHFIELLVPFFLFLGRRACIIHGVLQILFQAVLIVSGN	
	*.*** * .**.**** *** * * ***	
	MT PGPLSWFFHHLPKPLHRIEVAGNHFAQLVVPFGLFTPQPAASIAAAIIVVTQLWLVASGN	
10	HP LSFLNWLTMVPSLACFDDATLGFLFPSGPGSLKDRVLQMQRDIRGARPEPRFGSVVRRAA	
	.*.***** ***** *.*	
	MT FSWLNWLTILLACSAIDTSS-AAALLPMPAQPALSAPPQWFAGLVV	
	. HP NVSLGVLLAWLSVPVVLNLLSSRQVMNTHFNSLHIVNTYGAFGSITKERAEVILQGTASS	
15	*** ** . *****. * ** ** * ****** * ** *	
	MT VFTAAVLLLSYWPARNLLSSHQRMNMSFNPFHLVNTYGAFGSICRTRREVVIEGTDES	
	••••	
	HP NASAPDAMWEDYEFKCKPGDPSRRPCLISPYHYRLDWLMWFAAFQTYEHNDWIIHLAGKL	
	* . * * * * * * * * * * * * * *	
20	MT -PITEQTVWKAYEFKGKPGDPRRLPRQWAPYHLRLDWLMWFAAISPGYALPWMTPFLNRL	
	HP LASDAEALSLLAHNPFAGRPPPRWVRGEHYRYKFSRPGGRHAAEGKWWVRKRIGAYFPPL	
	* * * * * * * * * * * * * * * * * * * *	
	MT LRNDPATLKLLRHNPFP-QSPPRYVRAQLYQYRFTTVAELRRDRA-WWHRTLIGRYVPPM	
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HP SLEELRPYFRDRGWPLPGPL

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MT SLRKVASPPAD

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The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA019047) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03877> (SEQ ID NOS: 124, 134 and 144)

Determination of the whole base sequence of the cDNA insert of clone HP03877 obtained from cDNA library of human kidney revealed the structure consisting of a 106-bp 5'-untranslated region, a 1221-bp ORF, and a 678-bp 3'untranslated region. The ORF encodes a protein consisting of 406 amino acid residues and there existed four putative transmembrane domains. Figure 44 depicts ... the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 49 kDa that was somewhat larger than the molecular weight of 46,208 predicted from the ORF.

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The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to Caenorhabditis elegans hypothetical protein Y37D8A (Accession No. CAA21543). Table 31 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and Caenorhabditis elegans hypothetical protein Y37D8A (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 50.2% in the intermediate region of 329 amino acid residues.

15 Table 31

HP MAENG

CE MAKKOKKSTEKSERTVEFKEPPKPANSEERLVSTROFLAKIGOKKLIKKKVKNFRFSKKT

HP KNCDQRRVAMNKEHHNGNFTDPSSVNEKKRREREERQNIVLWRQPLITLQYFSLEILVIL

* ** ** * * * . . ** .

CE FIDFFSENQKKNCRLKPAGRGMKPSPSQNTLNRMERETIVFWRRPHIVIPYALMEIAHLA

25 HP KEWTSKLWHRQSIVVSFLLLLAVLIATYYVEGVHQQYVQRIEKQFLLYAYWIGLGILSSV 25

HP	GLGTGLHTFLLYLGPHIASVTLAAYECNSVNFPEPPYPDQIICPDEEGTEGTISLWSIIS
	. **. ******. **. ***. *
CE	GLGSGLHTFLIYLGPHIAAVTMAAYECQSLDFPQPPYPESIQCPSTKSSI-AVTFWQIVA
НP	KVRIEACMWGIGTAIGELPPYFMARAARLSGAEPDDEEYQEFEEMLEHAESAQDFA-
	.* ** ***. *********. ** *
CE	KVRVESLLWGAGTALGELPPYFMARAARISGQEPDDEEYREFLELMNADKESDADQKLSI
HP	-SRAKLAVQKLVQKVGFFGILACASIPNPLFDLAGITCGHFLVPFWTFFGATLIGKAIIK
	.*** * _. ** *** ********************
CE	VERAKSWVEHNIHRLGFPGILLFASIPNPLFDLAGITCGHFLVPFWSFFGATLIGKALVK
ΗР	MHIQKIFVIITFSKHIVEQMVAFIGAVPGIGPSLQKPFQEYLEAQRQKLHHKSEMGTPQG
	.*. *. **. *
CE	MHVQMGFVILAFSDHHAENFVKILEKIPAVGPYIRQPISDLLEKQRKALHKTPGEHSEQD
ΗР	ENWLSWMFEKLVVVMVCYFILSIINSMAQSYAKRIQQRLNSEEKTK
4	ENVESTING ENERTY MITCH TESTINGBINGS THAT THE SERVICE SERVICES AND ASSESSED ENTERTY.
CE	LIDEENQSFEEEEEAVTPPSSCPLLLSDGFEGVVVKK

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of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T18977) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10765> (SEQ ID NOS: 125, 135 and 145)

Determination of the whole base sequence of the cDNA insert of clone HP10765 obtained from cDNA library of human umbilical cord blood revealed the structure consisting of a 30-bp 5'-untranslated region, a 1362-bp ORF, and a 166-bp 3'-untranslated region. The ORF encodes a protein consisting of 453 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the inner portion. Figure 45 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 48 kDa that was almost identical with the molecular weight of 47,724 predicted from the ORF.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI792834) among ESTs. However, since they are partial sequences, it can not be judged whether or not they

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encode the same protein as the protein of the present invention.

<HP10766> (SEQ ID NOS: 126, 136 and 146)

Determination of the whole base sequence of the cDNA insert of clone HP10766 obtained from cDNA library of human kidney revealed the structure consisting of a 150-bp 5'-untranslated region, a 180-bp ORF, and a 675-bp 3'untranslated region. The ORF encodes a protein consisting of 59 amino acid residues and there existed two putative transmembrane domains. Figure 46 depicts hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In translation resulted in formation of a translation product of 10 kDa or less that was almost identical with the molecular weight of 6,098 predicted from the ORF.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T85491) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10770> (SEQ ID NOS: 127, 137 and 147)

Determination of the whole base sequence of the cDNA insert of clone HP10770 obtained from cDNA library of

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human kidney revealed the structure consisting of a 150-bp 5'-untranslated region, a 633-bp ORF, and a 186-bp 3'-untranslated region. The ORF encodes a protein consisting of 210 amino acid residues and there existed two putative transmembrane domains. Figure 47 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 27 kDa that was larger than the molecular weight of 22,156 predicted from the ORF.

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI792771) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10772> (SEQ ID NOS: 128, 138 and 148) *

Determination of the whole base sequence of the cDNA insert of clone HP10772 obtained from cDNA library of human kidney revealed the structure consisting of a 19-bp 5'-untranslated region, a 498-bp ORF, and a 724-bp 3'-untranslated region. The ORF encodes a protein consisting of 165 amino acid residues and there existed four putative transmembrane domains. Figure 48 depicts the

hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In translation resulted in formation of a translation product of high molecular weight.

5 The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. F11871) among ESTs. However, since they are partial sequences, it can not be judged whether or not they 10 encode the same protein as the protein of the present invention.

<HP10773> (SEQ ID NOS: 129, 139 and 149)

Determination of the whole base sequence of the cDNA insert of clone HP10773 obtained from cDNA library of human kidney revealed the structure consisting of a 186-bp 5'-untranslated region, a 489-bp ORF, and a 499-bp 3'untranslated region. The ORF encodes a protein consisting of 162 amino acid residues and there existed four putative transmembrane domains. Figure 49 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-20 -Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the GenBank using the base sequences 25 of the present cDNA has revealed the registration of

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sequences that shared a homology of 90% or more (for example, Accession No. N33828) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10776> (SEQ ID NOS: 130, 140 and 150) /

Determination of the whole base sequence of the cDNA insert of clone HP10776 obtained from cDNA library of human kidney revealed the structure consisting of a 207-bp 5'-untranslated region, a 666-bp ORF, and a 139-bp 3'-untranslated region. The ORF encodes a protein consisting of 221 amino acid residues and there existed three putative transmembrane domains. Figure 50 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 30 kDa that was larger than the molecular weight of 24,883 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI929639) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

INDUSTRIAL APPLICABILITY

The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, 5 expression vectors for these DNAs and eukaryotic cells expressing these DNAs. Since all of the proteins of the present invention are secreted or exist in the cell membrane, they are considered to be proteins controlling proliferation and/or the differentiation of the cells. 10 Accordingly, the proteins of the present invention can be employed as pharmaceuticals such as carcinostatic agents control the proliferation and/or differentiation of the cells, or as antigens for preparing antibodies against these proteins. The DNAs of the present 15 invention can be utilized as probes for the genetic diagnosis and gene sources for the gene therapy. Furthermore, the DNAs can be utilized for expressing these proteins in large quantities. Cells into which these genes introduced to express these proteins can be utilized for 20 detection of the corresponding receptors or ligands, screening of novel small molecule pharmaceuticals and the like. The antibody of the present invention can be utilized for the detection, quantification, purification and the like of the protein of the present invention.

The present invention also provides genes

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corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons; introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or information sequence the disclosed from primers identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, Trends Pharmacol. Sci. 15(7): 250-254;

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Lavarosky et al., 1997, Biochem. Mol. Med. 62(1): 11-22; and Hampel, 1998, Prog. Nucleic Acid Res. Mol. Biol. 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, Bioessays 14(9): 629-633; Zwaal et al., 1993, Proc. Natl. Acad. Sci. USA 90(16): 7431-7435; Clark et al., 1994, Proc. Natl. Acad. Sci. USA. 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination,

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preferably detected by positive/negative genetic selection strategies (Mansour et al., 1988, Nature 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s). Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the identified in accordance with known invention can be techniques for determination of such domains from sequence information.

proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed

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protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is,

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naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Table 32

Stringency	Poly-	Hybrid	Hybridization Temperature	Wash
Condition	nucleotide	Length	and Buffer'	Temperature
	Hybrid	(bp) *		and Buffer'
A	DNA: DNA	≥50	65°C; 1×SSC -or-	65°C;
			42°C; 1×SSC,50%	0.3×SSC
			formamide	
В	DNA: DNA	<50	T ₈ *; 1×SSC	T _s *; 1×SSC
С	DNA: RNA	≥50	67°C; 1×SSC -or-	67°C;
			45°C; 1×SSC,50%	0.3×SSC
		•	formamide	
D	DNA: RNA	<50	T _D *; 1×SSC	Tp*; 1×SSC
E	RNA: RNA	≥50	70°C; 1×SSC -or-	70°C;
_			50°C; 1×SSC,50%	0.3×SSC
	·	<u> </u>	formamide	
F	RNA: RNA	<50	T _F *; 1×SSC	T _F *; 1×SSC
G	DNA: DNA	≥50	65°C; 4×SSC -or-	65°C; 1×SSC
	1		42°C; 4×SSC,50%	
			formamide	<u></u>
Н	DNA: DNA	<50	T _H *; 4×SSC	T _H *; 4×SSC
I	DNA: RNA	≥50	67°C; 4×SSC -or-	67°C; 1×SSC
		-	45°C; 4×SSC,50%	
			formamide	
J	DNA: RNA	<50	T _J *; 4×SSC	T _J *; 4×SSC
K.	RNA: RNA	≥50	70°C; 4×SSC -or-	67°C; 1×SSC
			50°C; 4×SSC,50%	ļ
			formamide	
L	RNA: RNA	< 50 .	T _L *; 2×SSC	T _L *; 2×SSC
М	DNA: DNA	≥50	50°C; 4×SSC -or-	50°C; 2×SSC
	. •		40°C; 6×SSC,50%	
			formamide	
N	DNA: DNA	< 50	T _N *; 6×SSC	T _N *; 6×SSC
0	DNA: RNA	≥50	55°C; 4×SSC -or-	55°C; 2×SSC
			42°C; 6×SSC,50%	
			formamide	
, P	DNA: RNA	<50	T _p *; 6×SSC	Tp*; 6×SSC
Q	RNA: RNA	≥50	60°C; 4×SSC -or-	60°C; 2×SSC
	. :	•	45°C; 6×SSC,50%	
			formamide	
R	RNA: RNA	<50	T _R *; 4×SSC	T _R *; 4×SSC

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- t: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.
- t: SSPE (1×SSPE is 0.15M NaCl, 10mM NaH₂PO₄, and 1.25mM EDTA, pH7.4) can be substituted for SSC (1×SSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.
- 15 *T_B T_R: The hybridization temperature for hybrids
 anticipated to be less than 50 base pairs in length should
 be 5-10°C less than the melting temperature (T_m) of the
 hybrid, where T_m is determined according to the following
 equations. For hybrids less than 18 base pairs in length,
 20 T_m(°C)=2(#of A + T bases) + 4(# of G + C bases). For hybrids
 between 18 and 49 base pairs in length, T_m(°C)=81.5 +
 16.6(log₁₀[Na⁺]) + 0.41 (%G+C) (600/N), where N is the
 number of bases in the hybrid, and [Na⁺] is the concentration
 of sodium ions in the hybridization buffer ([Na⁺] for
 25 1×SSC=0.165M).

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Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

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CLAIMS

- 1. A protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100 and 121 to 130.
- 2. An isolated DNA encoding the protein according to Claim 1.
- 3. An isolated cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID NOS: 11 to 20, 41 to 50, 71 to 80, 101 to 110 and 131 to 140.
 - 4. The cDNA according to Claim 3 consisting of any one of a base sequence selected from the group consisting of SEQ ID NOS: 21 to 30, 51 to 60, 81 to 90, 111 to 120 and 141 to 150.
- 5. An expression vector that is capable of expressing the DNA according to any one of Claim 2 to Claim 4 by in vitro translation or in eukaryotic cells.
 - 6. A transformed eukaryotic cell that is capable of expressing the DNA according to any one of Claim 2 to Claim 4 and of producing the protein according to Claim 1.
 - 7. An antibody directed to the protein according to Claim 1.

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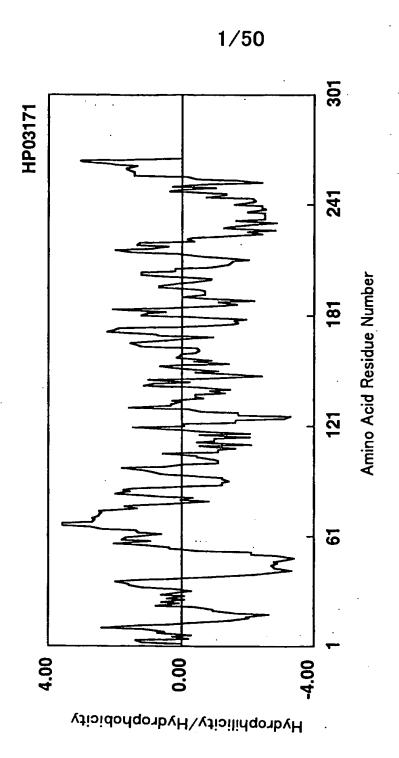


Fig. 1

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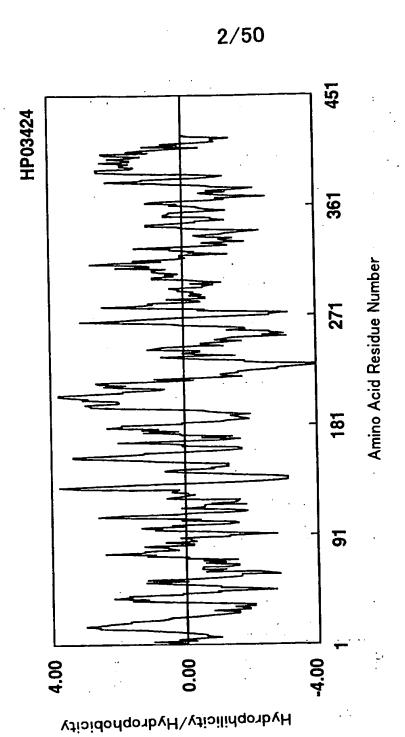


Fig.2

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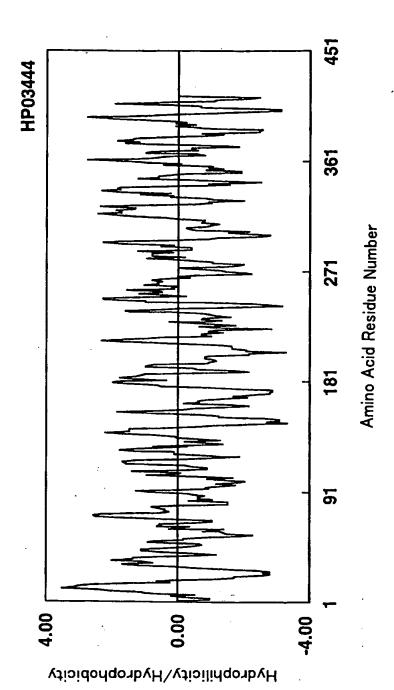
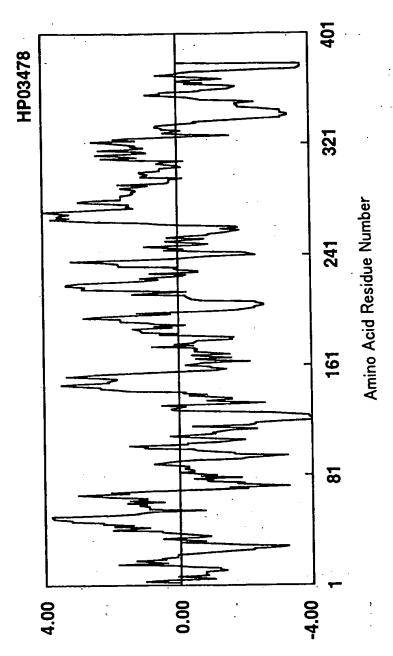


Fig.3





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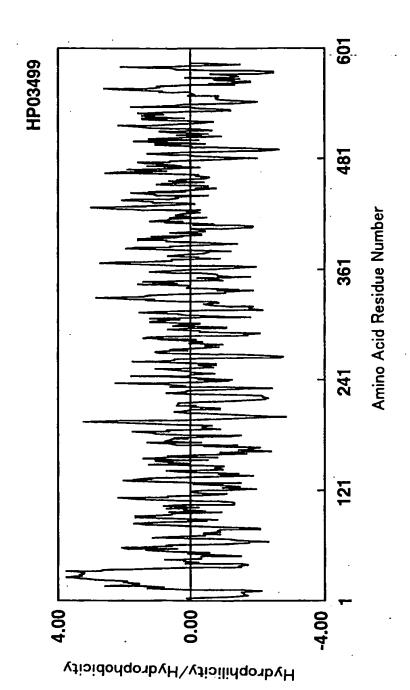
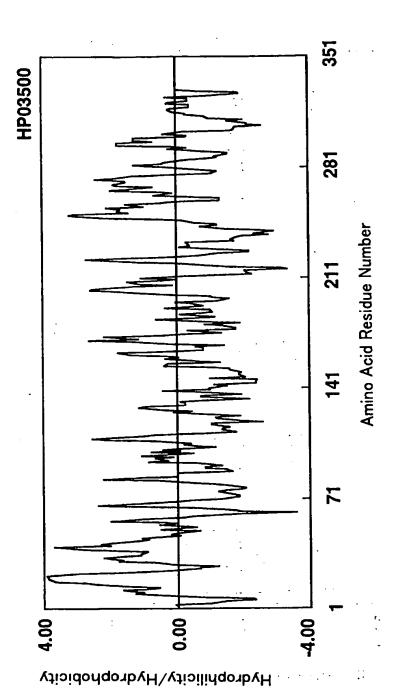


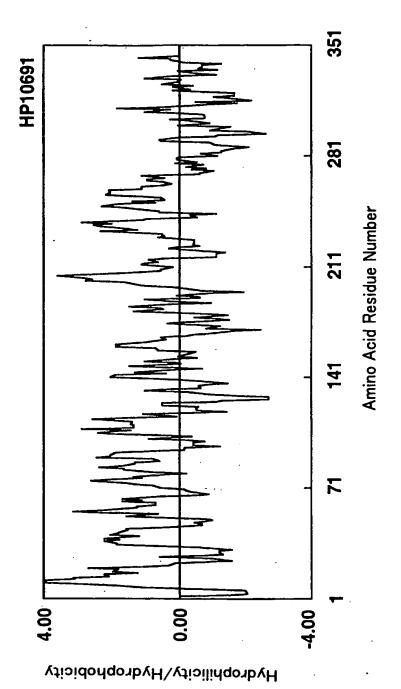
Fig.5

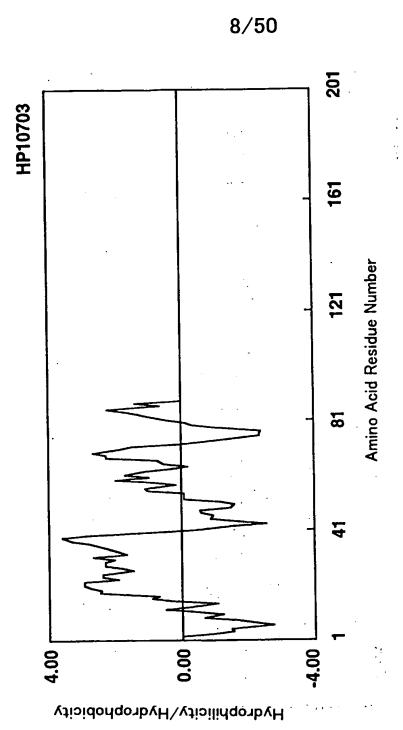




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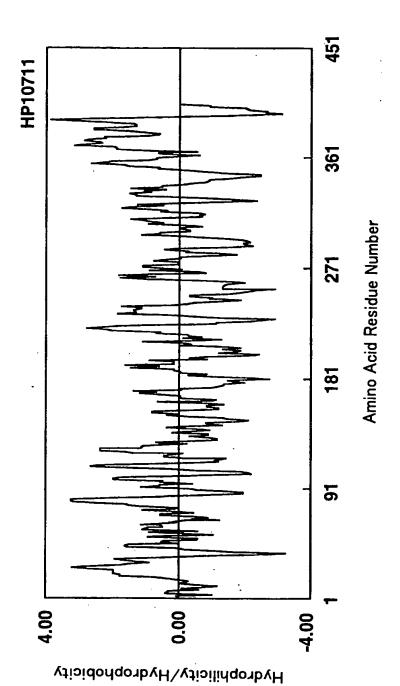
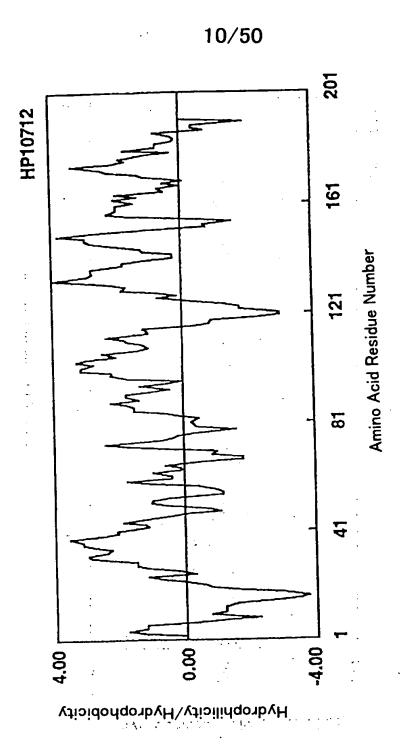


Fig.9

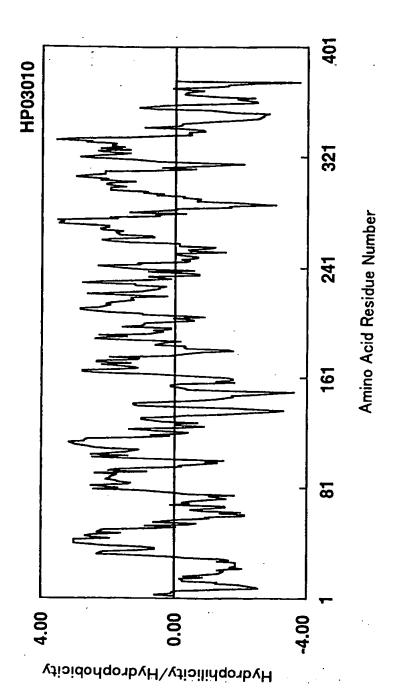
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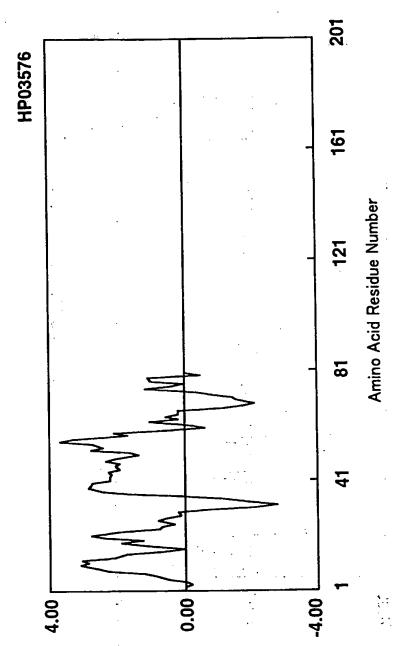
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Hydrophilicity/Hydrophobicity

Fig. 12

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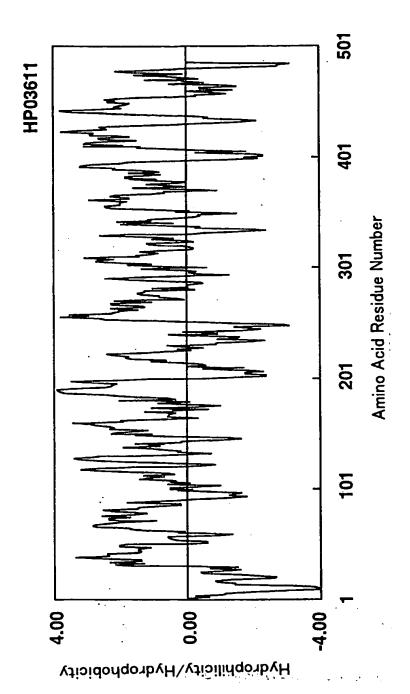


Fig. 13



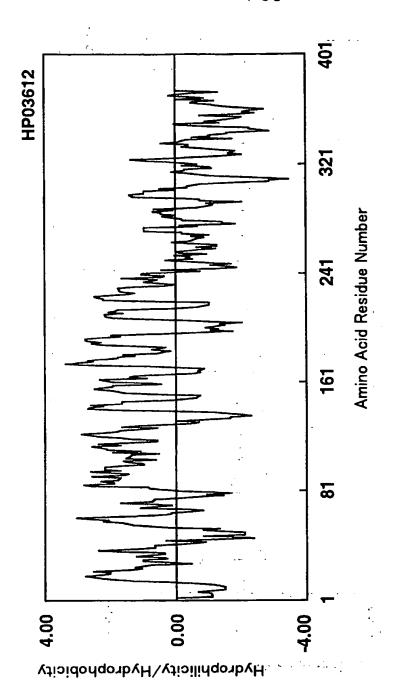


Fig.14



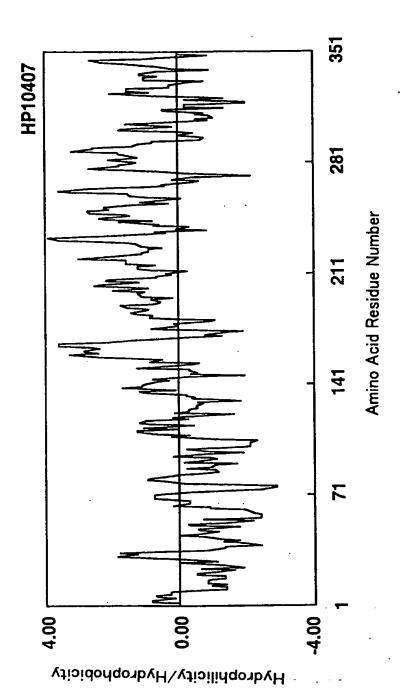


Fig. 15



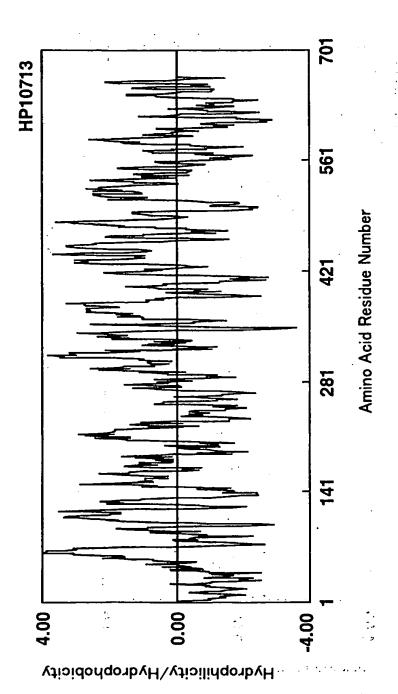


Fig.16

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والمراجون أجراني



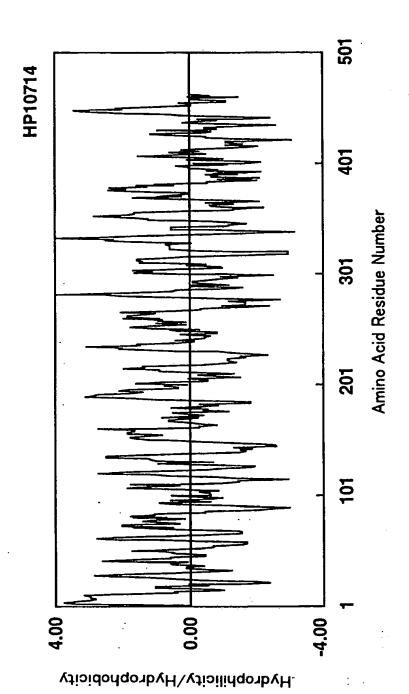
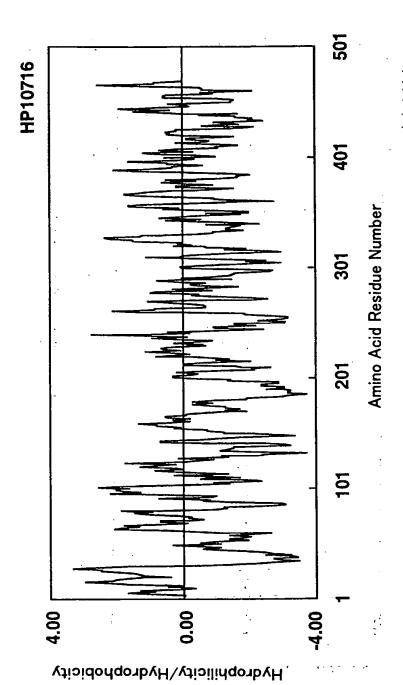


Fig. 17

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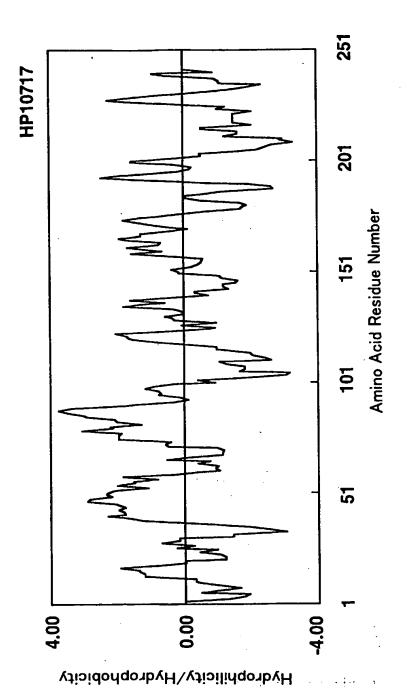
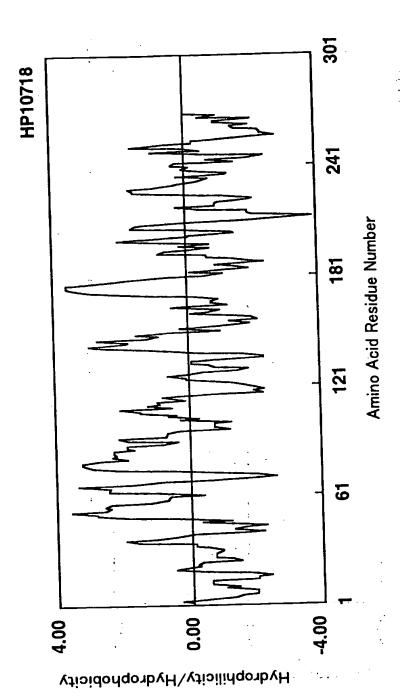


Fig. 19



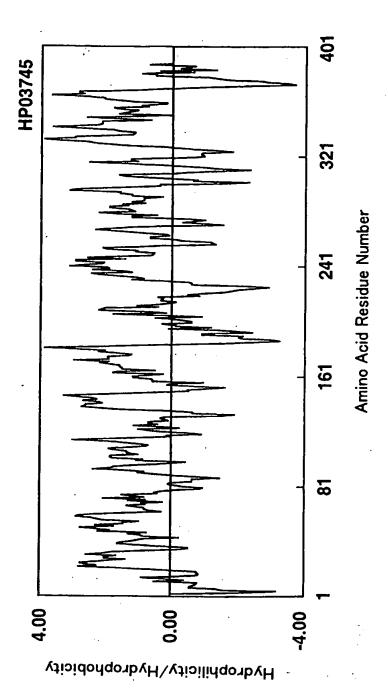


Fig.21

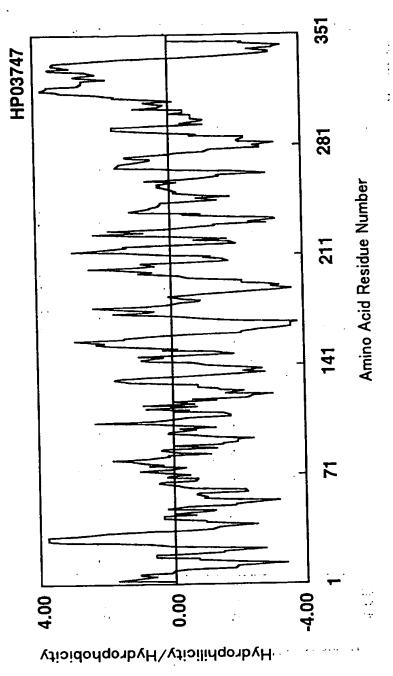


Fig.22

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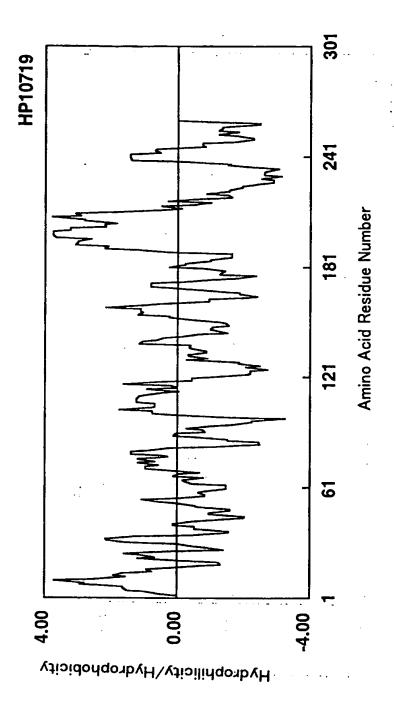


Fig.23



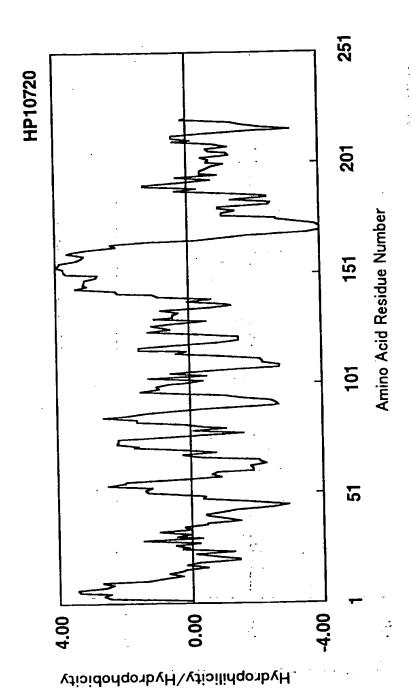


Fig.24

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The section of the section of



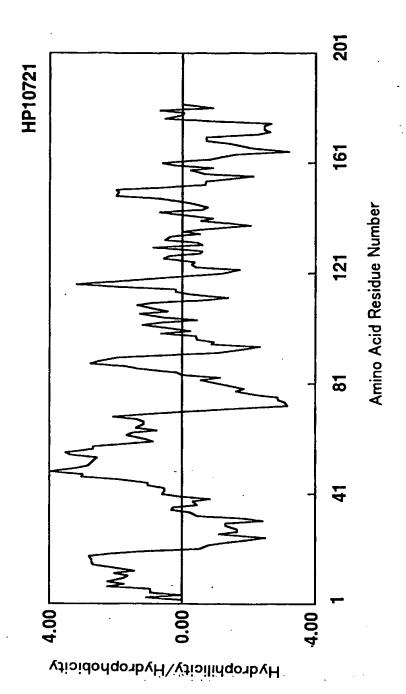


Fig. 25

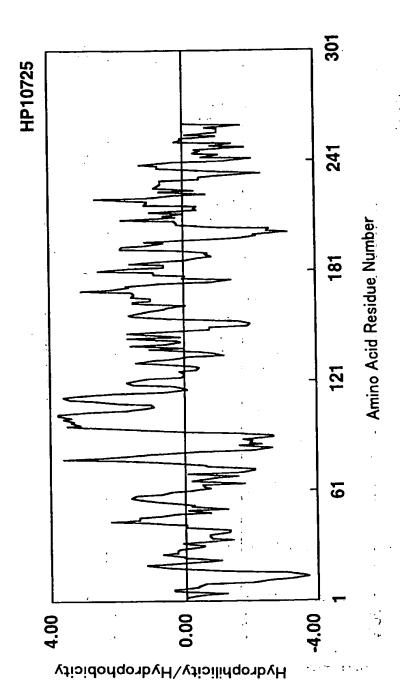
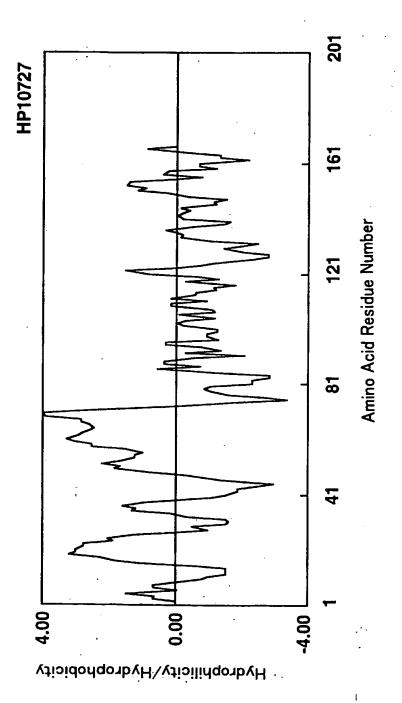


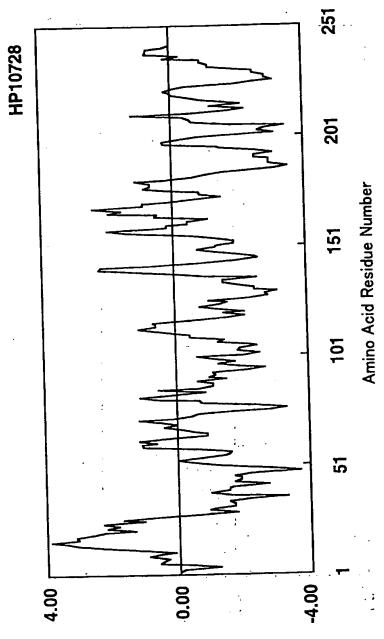
Fig.26

1 1 1 1 mm

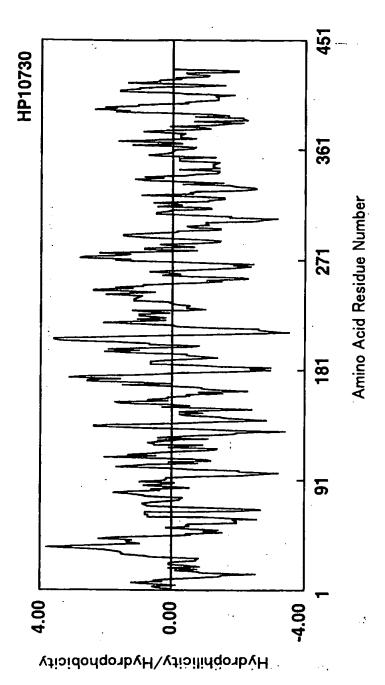
BNSDOCID- WO 011266042 I 5







Hydrophilicity/Hydrophobicity.



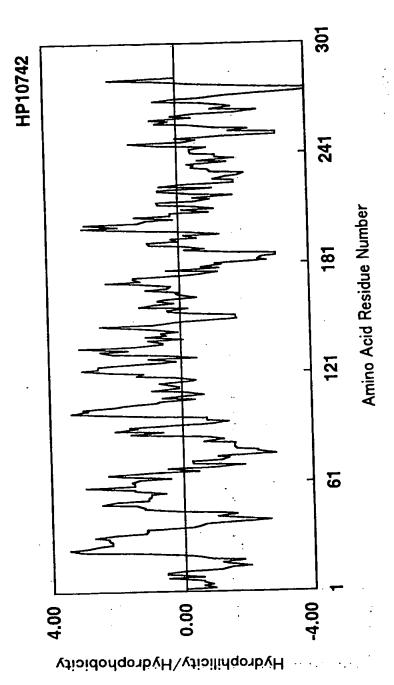
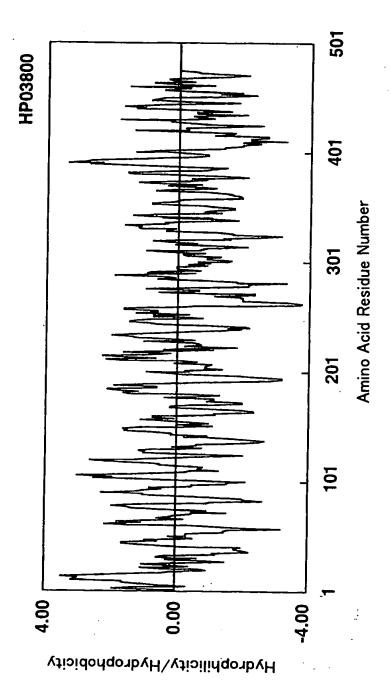
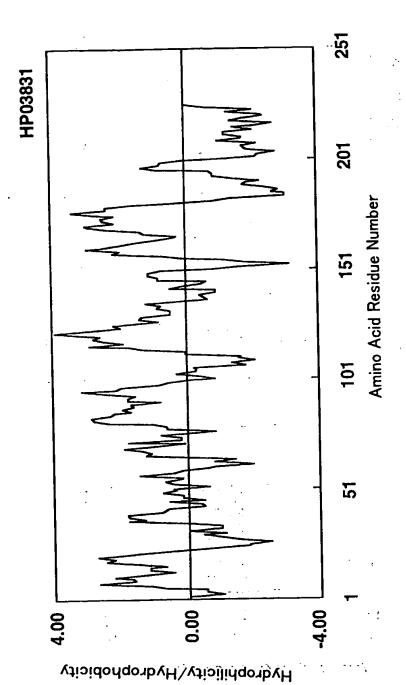


Fig.30

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-ig.31



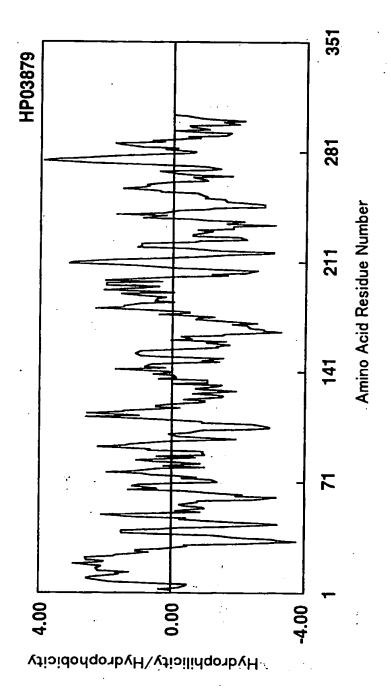


Fig.33

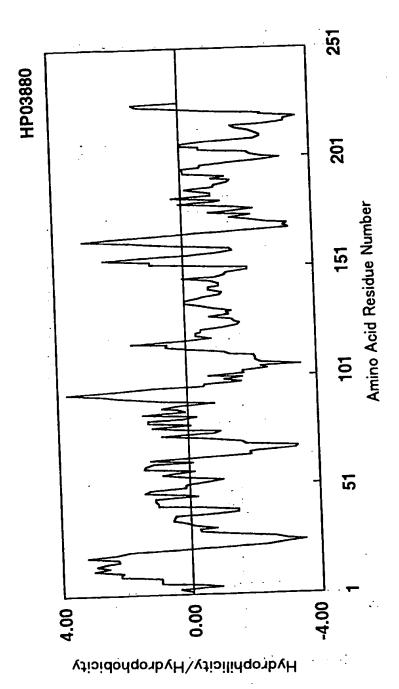
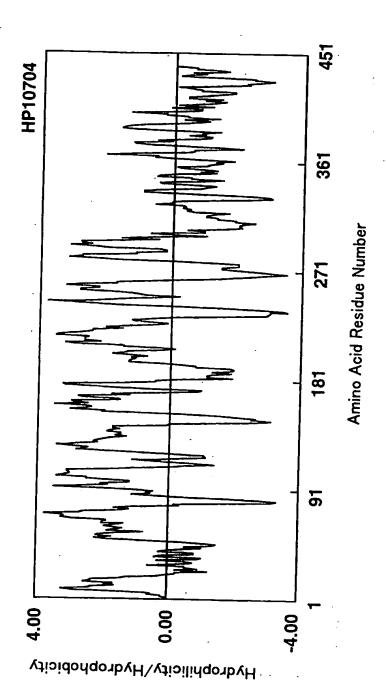


Fig.34

DYIGUULU -MIU UTTSEEURS T -



ig.35

ENGULCIU- MU UTTSEEURS I

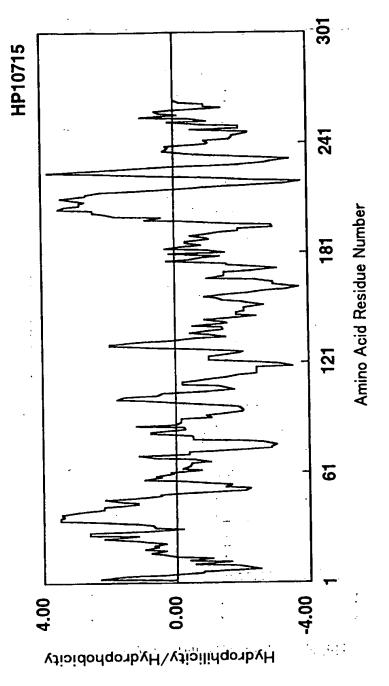


Fig.36

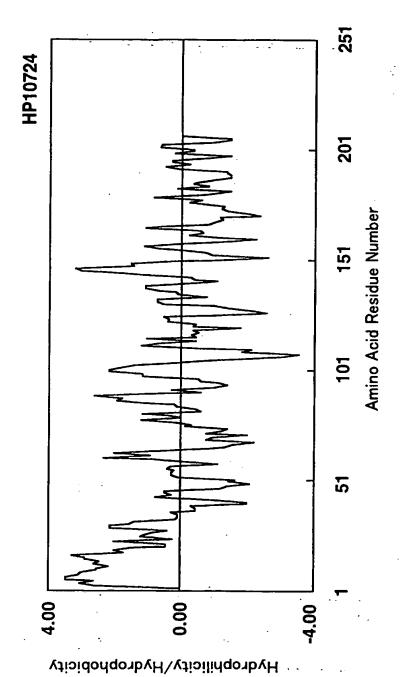


Fig.37

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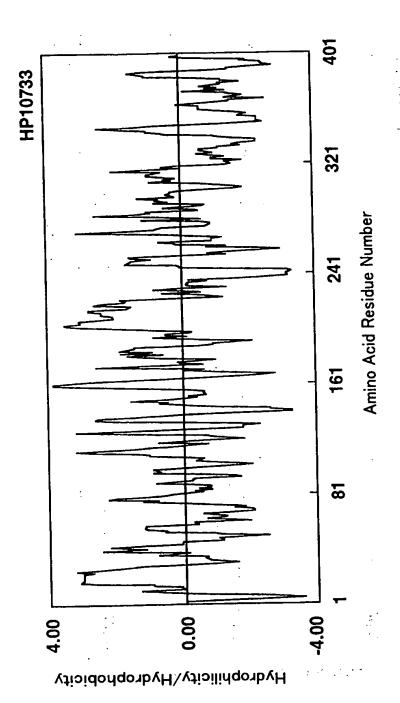
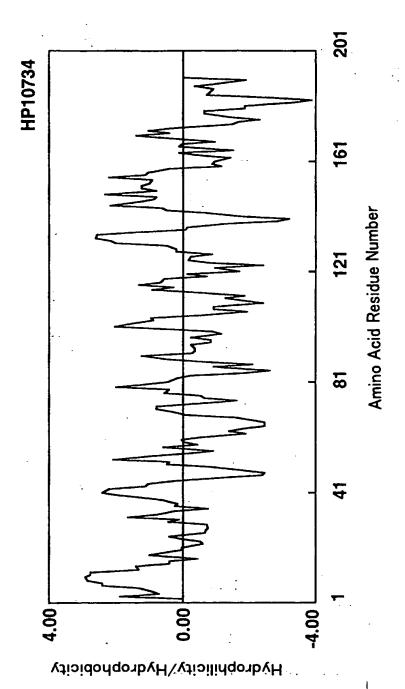


Fig.38



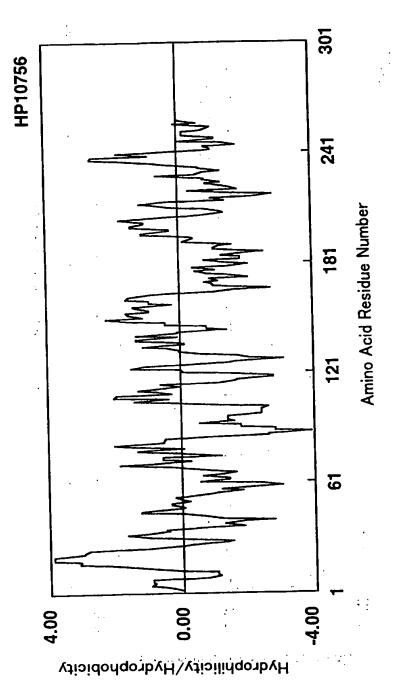
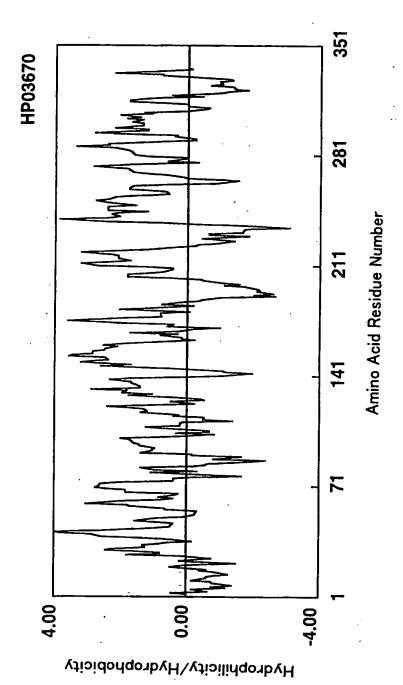
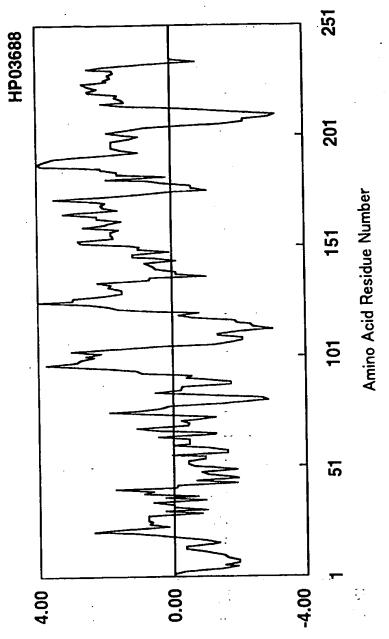


Fig. 40



ig.41



Hydrophilicity/Hydrophobicity

Fig. 42



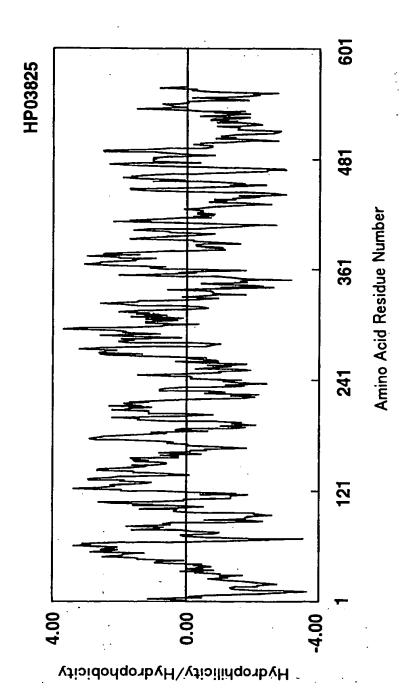


Fig.43

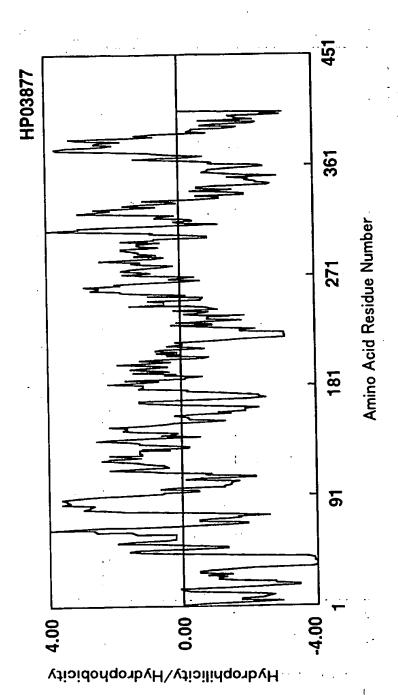


Fig.44

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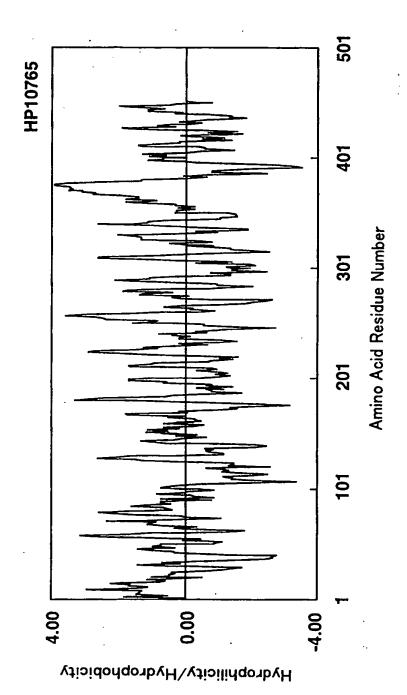
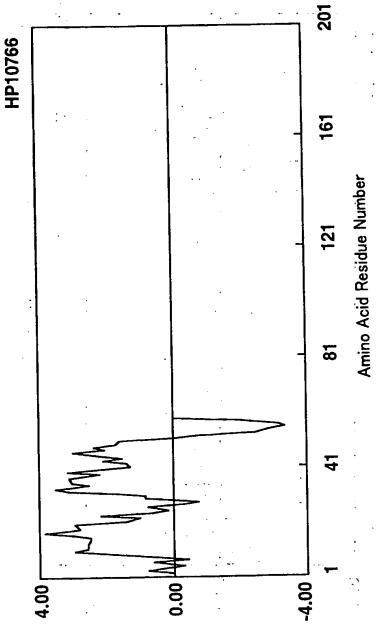


Fig. 45





Hydrophilicity/Hydrophobicity

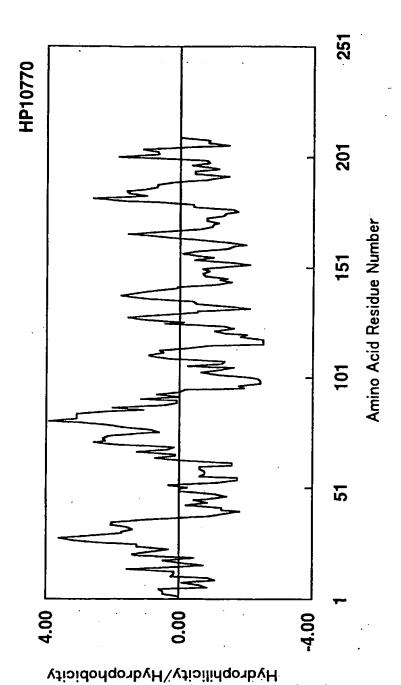
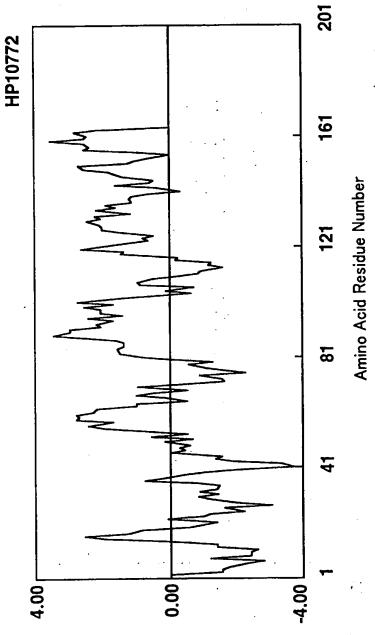
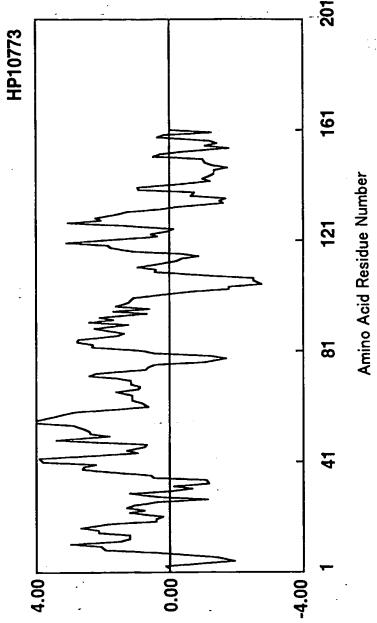


Fig. 47

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Ηλqrophilicity/Ηγdrophobicity



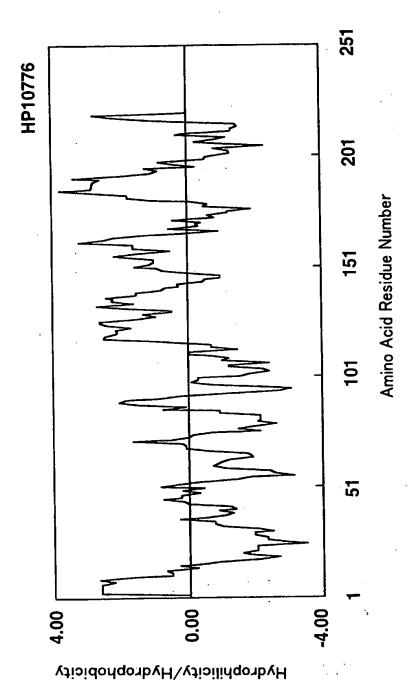
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Hydrophilicity/Hydrophobicity

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•	nia	1ys 35													
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		115					120					125		:	
Leu	Leu	Lys	Lys	Phe	Arg	Glu	Ala	Ser	Trp	Arg	Phe	Thr	Phe	Tyr	Leu
	130					135		· .			140				
Ile	Ala	Phe	Ile	Ala	Gly	Met	Ala	Val	Ile	Val	Asp	Lys	Pro	Trp	Phe
145					150					155					160
Tyr	Asp	Met	Lys	Lys	Val	Trp	Glu	Gly	Tyr	Pro	Ile	Gln	Ser	Thr	Ile
				165					170					175	
Pro	Ser	Gln	Tyr	Trp	Tyr	Tyr	Met	Ile	Glu	Leu	Ser	Phe	Tyr	Trp	Ser
			180					185					190		
Leu	Leu	Phe	Ser	Ile	Ala	Ser	Asp	Val	Lys	Arg	Lys	Asp	Phe	Lys	Glu
		195					200					205			
Gln	Ile	Ile	His	His	Val	Ala	Thr	Ile	Ile	Leu	Ile	Ser	Phe	Ser	Trp
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Phe	Ala	Asn	Tyr	Ile	Arg	Ala	Gly	Thr	Leu	Ile	Met	Ala	Leu	His	Asp
225	•				230					235					240
Ser	Ser	Asp	Tyr	Leu	Leu	Glu	Ser	Ala	Lys	Met	Phe	Asn	Tyr	Ala	Gly
٠,			:	245			٠.,		250		٠.		٠.	255	
Trp	Lys	Asn	Thr	Cys	Asn	Asn	Ile	Phe	Ile	Val	Phe	Ala	Ile	Val	Phe
;*,	•	`.	260			٠,,	٠.	265	•		. •		270		. :
Ile	Ile	Thr	Arg	Leu	Val	Ile	Leu	Pro	Phe	Trp	Ile	Leu	His	Cys	Thr
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Leu Val Ty	r	Pro	Leu	Glu	Leu	Tyr	Pro	Ala	Phe	Phe	Gly	Tyr	Tyr	Phe
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Phe Asn Se	r	Met	Met	Gly	Val	Leu	Gln	Leu	Leu	His	Ile	Phe	Trp	Ala
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Tyr Leu Il	.e	Leu	Arg	Met	Ala	His	Lys	Phe	Ile	Thr	Gly	Lys	Leu	Val
• • •		•	325					330		,	٠.		335	•
Glu Asp G	u	Arg	Ser	Asp	Arg	Glu	Glu	Thr	Glu	Ser	Ser	Glu	Gly	Glu
		340				1	345					350	~	٠
Glu Ala A	la	Ala	Gly	Gly	Gly	Ala	Lys	Ser	Arg	Pro	Leu	Ala	Asn	Gly
<u>:</u> 3!	55	•	•		•	360		٠.	•		365			
His Pro I	le	Leu	Asn	Asn	Asn	His	Arg	Lys	Asn	Asp				
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Ala Gly I	le	Thr	Cys	Val	Sei	· Val	Va!	Va]	l Ile	Ala	Ala	ı Ile	e Val	Leu
•		20)		•		25	5 .			v.	30)	
Ala Ile 7	hr	Leu	ı Arg	g Arg	g Pro	Gly	, 'Cy:	s Glı	ı Lei	ı Glu	ı Ala	а Су:	s Sei	Pro
	35			<i>:</i> ,	٠.	40)				4	5	٠.	· • • •
Asp Ala A	۱sp	Met	t Le	ı Ası	р Ту	r Lei	u Lei	u Se:	r Lei	u Gl	y G1:	n Il	e 'Sei	r Arg

	50				•	55					60			٠	
Arg	Asp	Ala	Leu	Glu	Val	Thr	Trp	Tyr	His	Ala	Ala	Asn	Ser	Lys	Lys
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Ala	Met	Thr	Ala	Ala	Leu	Asn	Ser	Asn	Ile	Thr	Val	Leu	Glu	Ala	Asp
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Val	Asn	Val	Glu	Gly	Leu	Gly	Thr	Ala	Asn	Glu	Thr	Gly	Val	Pro	Ile
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Met	Ala	His	Pro	Pro	Thr	Ile	Tyr	Ser	Asp	Asn	Thr	Leu	Glu	Gln	Trp
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Leu	Asp	Ala	Val	Leu	Gly	Ser	Ser	Gln	Lys	Gly	Ile	Lys	Leu	Asp	Phe
	130					135					140				
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145					150					155					160
Thr	Glu	Glu	Gly	Lys	Val	Arg	Arg	Pro	Ile	Trp	Ile	Asn	Ala	Asp	Ile
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Gln	Ala	Met	Val	Glu	Lys	Met	His	Glu	Leu	Val	Gly	G1y	Val	Pro	Gln
225		. •		•	230		Ϋ,.	~·.	ď.	235	: ,			: •	240
Arg	Val	Thr	Phe	Pro	Val	Arg	Ser	Ser	Met	Val	Arg	Ala	Ala	Trp	Pro
ł.	,		٠.	245			٠.,		250					255	

His	Phe	Ser	Trp	Leu	Leu	Ser	Gln	Ser	Glu	Arg	Tyr	Ser	Leu	Thr	Leu
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Trp	Gln	Ala	Ala	Ser	Asp	Pro	Met	Ser	Val	Glu	Asp	Leu	Leu	Tyr	Val
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Arg	Asp	Asn	Thr	Ala	Val	His	Gln	Val	Tyr	Tyr	Asp	Ile	Phe	Glu	Pro
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Leu	Leu	Ser	Gln	Phe	Lys	Gln	Leu	Ala	Leu	Asn	Ala	Thr	Arg	Lys	Pro
305		ر			310			-	d.	315		•	•		320
Met	Tyr	Tyr	Thr	Gly	Gly	Ser	Leu	Ile	Pro	Leu	Leu	Gln	Leu	Pro	Gly
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Asp	Asp	Gly	Leu	Asn	Val	Glu	Trp	Leu	Val	Pro	Asp	Val	Gln	Gly	Ser
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Gly	Lys	Thr	Ala	Thr	Met	Thr	Leu	Pro	Asp	Thr	Glu	Gly	Met	Ile	Leu
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Leu	Asn	Thr	Gly	Leu	Glu	Gly	Thr	Val	Ala	Glu	Asn	Pro	Val	Pro	Ile
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385					390		,		٠	395					400
Gln	. Leu	Ala	Thr	His	Pro	Gly	His	Trp	Gly	Ile	His	Leu	G1n	Ile	Ala
				405	;				410	•				415	; · ·
Glu	ı Pro	Ala	. Ala	Leu	Arg	Pro	Ser	Leu	Ala	Leu	Leu	Ala	Arg	Leu	Ser
			420) .			-	425	;				430	γ	
Sei	r Lei	ı Gly	/ Leu	ı Leu	ı His	Trp	Pro	Val	Trp	Val	Gly	Ala	Lys	Ile	Ser
	•														
Нi	s (61s	i Sei	r Pha	e Ser	- Val	Pro	Glv	, His	; Val	Ala	ı Glv	Ars	g Glu	ı Let	ı Leu

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Control of the state of

450 455	460
Thr Ala Val Ala Glu Val Phe Pro His	Val Thr Val Ala Pro Gly Trp
465 470	475 480
Pro Glu Glu Val Leu Gly Ser Gly Tyr	Arg Glu Gln Leu Leu Thr Asp
485	490 495
Met Leu Glu Leu Cys Gln Gly Leu Trp	Gln Pro Val Ser Phe Gln Met
500 505	510
Gln Ala Met Leu Leu Gly His Ser Thr	Ala Gly Ala Ile Gly Arg Leu
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Leu Ala Ser Ser Pro Arg Ala Thr Val	Thr Val Glu His Asn Pro Ala
530 535	540
Gly Gly Asp Tyr Ala Ser Val Arg Thr	Ala Leu Leu Ala Ala Arg Ala
545 550	555 560
Val Asp Arg Thr Arg Val Tyr Tyr Arg	Leu Pro Gln Gly Tyr His Lys
565	570 575
Asp Leu Leu Ala His Val Gly Arg Asn	
580 585	to the second second
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Met Trp Leu Trp Glu Asp Gln Gly Gly	
$(1_{\frac{1}{4},\frac{1}{4}},\ldots,1_{\frac{1}{4}},\ldots,\frac{1}{4}$. 10

Leu	Leu	Leu	Val	Leu	Leu	Leu	Val	Thr	Arg	Ser	Pro	Val	Asn	Ala	Cys
		,	20				٠.	25					30		
Leu	Leu	Thr	Gly	Ser	Leu	Phe	Val	Leu	Leu	Arg	Val	Phe	Ser	Phe	Glu
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Pro	Val	Pro	Ser	Cys	Arg	Ala	Leu	G1n	Val	Leu	Lys	Pro	Arg	Asp	Arg
	50			•		55					60		-		1
Ile	Ser	Ala	Ile	Ala	His	Arg	Gly	Gly	Ser	His	Asp	Ala	Pro	Glu	Asn
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Thr	Leu	Ala	Ala	Ile	Arg	Gln	Ala	Ala	Lys	Asn	G1y	Ala	Thr	Gly	Val
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Glu	Leu	Asp	Ile	Glu	Phe	Thr	Ser	Asp	Gly	Ile	Pro	Val	Leu	Met	His
	• • •		100	٠				105			•		110		
Asp	Asn	Thr	Val	Asp	Arg	Thr	Thr	Asp	Gly	Thr	Gly	Arg	Leu	Cys	Asp
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Leu	Thr	Phe	Glu	Gln	Ile	Arg	Lys	Leu	Asn	Pro	Ala	Ala	Asn	His	Arg
	130					135		٠.		٠	140			•	•.
Leu	Arg	Asn	Asp	Phe	Pro	Asp	Glu	Lys	Ile	Pro	Thr	Leu	Arg	Glu	Ala
145					150					155					160
Val	Ala	Glu	Cys	Leu	Asn	His	Asn	Leu	Ţhr	Ile	Phe	Phe	Asp	Val	Lys
				165					170					175	•
Gly	His	Ala	His	Lys	Ala	Thr	Glu	Ala	Leu	Lys	Lys	Met	Tyr	Met	Glu
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Phe	Pro	Gln	Leu	Tyr	Asn	Asn	Ser	Val	Val	Cys	Ser	Phe	Leu	Pro	Glu
, **		195				•	200					205	•	•	
Val	Ile	Tvr	Lvs	Met	Arg	Gln	Thr	Asp	Arg	Asp	Val	Ile	Thr	Ala	Leu

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Thr His Arg Pro 1	Irp Ser Leu Se	r His Thr Gly	Asp Gly Lys Pro Arg
225	230	235	240
Tyr Asp Thr Phe 1	Trp Lys His Ph	e Ile Phe Val	Met Met Asp Ile Leu
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Leu Asp Trp Ser M	Met His Asn Il	e Leu Trp Tyr	Leu Cys Gly Ile Ser
260		265	270
Ala Phe Leu Met (Gln Lys Asp Ph	e Val Ser Pro	Ala Tyr Leu Lys Lys
275	28	0	285
Trp Ser Ala Lys (Gly Ile Gln Va	l Val Gly Trp	Thr Val Asn Thr Phe
290	295		300
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Gly Ala Ala Ala Val Gly	Leu Gly Leu	Thr Leu Phe T	hr Cys Gly Pro	0
	40		45	
His Thr Leu His Ser Leu	Val The Ile	Leu Glv Thr T	rp Ala Leu Il	.e ·
		60		
50				
Gln Ala Gln Pro Cys Ser	Cys His Ala	Leu Ala Leu A	lla Trp Inr Pi	16
65 70	• • •	75	· · · · · · · · · · · · · · · · · · ·	80
Ser Tyr Leu Leu Phe Phe	Arg Ala Leu	Ser Leu Leu	Gly Leu Pro T	hr
85		90		:
Pro Thr Pro Phe Thr Asr	ı Ala Val Gln	Leu Leu Leu	Thr Leu Lys L	eu,
100	105		110	
Val Ser Leu Ala Ser Gl				_ys
115	120		125	•
Glu Met Ala Ser Gly Ph	e Ser Lys Gl	y Pro Thr Leu	Gly Leu Leu	Pro
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Asp Val Pro Ser Leu Me	et Glu Thr Le	eu Ser Tyr Ser	Tyr Cys Tyr	Val
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Gly Ile Met Thr Gly P	ro Phe Phe A	rg Tyr Arg Thi	r Tyr Leu Asp	Trp
165		170	175	
Leu Glu Gln Pro Phe P	ro Gly Ala V	al Pro Ser Le	u Arg Pro Leu	Leu
180		85	190	
Arg Arg Ala Trp Pro	Ala Pro Leu F	he Gly Leu Le	eu Phe Leu Leu	ı Ser
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Ser His Leu Phe Pro	Leu Glu Ala '	Val Arg Glu A	sp Ala Phe Ty	r Ala
210	215	2	20	. 1 63
Arg Pro Leu Pro Ala	Arg Leu Phe	Tyr Met Ile P	ro Val Phe Ph	e Ala

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225	230	235	240
Phe Arg Met Arg	Phe Tyr Val Al	a Trp Ile Ala Ala	Glu Cys Gly Cys
. ,	245	250	255
Ile Ala Ala Gly	Phe Gly Ala Ty	r Pro Val Ala Ala	Lys Ala Arg Ala
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Gly Gly Gly Pro	Thr Leu Gln Cys	s Pro Pro Pro Ser	Ser Pro Glu Lvs
275	280	•	285
Ala Ala Ser Leu	Glu Tyr Asp Tyr	Glu Thr Ile Arg A	Asn Ile Asp Cvs
290	295	300	•
Tyr Ser Thr Asp	Phe Cys Val Arg	Val Arg Asp Gly M	let Arg Tyr Trp
305	310	315	320
Asn Met Thr Val	Gln Trp Trp Leu	Ala Gln Tyr Ile T	•
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Pro Ala Arg Ser			335
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Phe Phe Phe Val G	y Val Leu Phe S	er Ala Val Ser Ile	Ala Ala Phe
		25 ,	

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_								en i			~1	C	•	TL	
		Phe		Val	Leu	Ala	He	Ihr	Arg	HIS	GIN	Ser	Leu	ınr	ASP
	••	35					40				-	45			•
Pro	Thr	Ser	Tyr	Tyr	Leu	Ser	Ser	Val	Trp	Ser	Phe	Ile	Ser	Phe	Lys
	50	•:				55					60	i		. •	
Trp	Ala	Phe	Leu	Leu	Ser	Leu	Tyr	Ala	His	Arg	Tyr	Arg	Ala	Asp	Phe
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Ala	Asp	Ile	Ser	Ile	Leu	Ser	Asp	Phe							
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		Leu	Len			Thr	Len	Leu			Ala	Ala	Pro	Phe	Gly
Jei		LCG	20					25		• • • • • • • • • • • • • • • • • • • •			30		•
-		01			~ L_	4	. c1_			Laur	C1	Vo.1		Dro	Acn
Leu	Let	ı Gly		Lys	inr	Arg			Ser	Leu	Glu			110	,
		35	5				40	•				45	•		
Trp	Lei	ı Gly	r Pro	Leu	G1n	Asn	Leu	Leu	His	Ile	Arg	Ala	Val	Gly	Thr
	50	כ	, ,	•		55			·*·		60				
Asn	Se:	r Thi	Leu	His	Tyr	Val	Trp	Ser	Ser	Leu	Gly	Pro	Leu	Ala	Val
65	5		• • •	•	70)				75	; ·		:		80
Va1	Ma	t Val	<u> </u>	The	· Acr	The	· Pro	Hic	: Set	- Thi	· Lei	ı Sei	· Val	Asn	Trp

			85					90					95	
Ser Leu	Leu	Leu	Ser	Pro	Glu	Pro	Asp	Gly	Gly	Leu	Met	Val	Leu	Pro
		100	•		-		105					110		•
Lys Asp	Ser	Ile	Gln	Phe	Ser	Ser	Ala	Leu	Val	Phe	Thr	Arg	Leu	Leu
	115					120					125			
Glu Phe	Asp	Ser	Thr	Asn	Val	Ser	Asp	Thr	Ala	Ala	Lys	Pro	Leu	Gly
130					135					140				
Arg Pro	Tyr	Pro	Pro	Tyr	Ser	Leu	Ala	Asp	Phe	Ser	Trp	Asn	Asn	Ile
145				150					155					160
Thr Asp	Ser	Leu	Asp	Pro	Ala	Thr	Leu	Ser	Ala	Thr	Phe	Gln	Gly	His
			165					170					175	
Pro Met	Asn	Asp	Pro	Thr	Arg	Thr	Phe	Ala	Asn	Gly	Ser	Leu	Ala	Phe
		180					185					190		
Arg Val	Gln	Ala	Phe	Ser	Arg	Ser	Ser	Arg	Pro	Ala	Gln	Pro	Pro	Arg
	195					200					205	٠.		
Leu Leu	His	Thr	Ala	Asp	Thr	Cys	Gln	Leu	Glu	Val	Ala	Leu	Ile	Gly
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Ala Ser	Pro	Arg	Gly	Asn	Arg	Ser	Leu	Phe	Gly	Leu	Glu	Val	Ala	Thr
225				230					235					240
Leu Gly	Gln	Gly	Pro	Asp	Cys	Pro	Ser	Met	Gln	Glu	Gln	His	Ser	Ile
			245					250			÷		255	• .
Asp Asp	Glu	Tyr	Ala	Pro	Ala	Val	Phe	Gln	Leu	Asp	Gln	Leu	Leu	Trp
	٠,	260	.: •		,	. ;	265 ,		1.1.1		··· ,	270	٠,.	• •
Gly Ser	Leu	Pro	Ser	Gly	Phe	Ala	Gln	Trp	Arg	Pro	Val	Ala	Tyr	Ser
egar j	275	Į (; ,	. ,	; , 3	280	4	. ~ .	: · .		285			

Gln L	ys.	Pro	Gly	Gly	Arg	Glu	Ser	Ala	Leu	Pro	Cys	Gln	Ala	Ser	Pro	
2	90	•,	•	•	•	295	٠	,	•		300		•	•		•
Leu H	lis	Pro	Äla	Leu	Ala	Tyr	Ser	Leu	Pro	Gln	Ser	Pro	Ile	Val	Arg	
305					310	•			٠	315	•		•		320	
Ala P	he	Phe	Gly	Ser	Gln	Asn	Asn	Phe	Cys	Ala	Phe	Asn	Leu	Thr	Phe	
		٠		325			-		330	•				335	. •	
Gly A	lla	Ser	Thr	Gly	Pro	Gly	Tyr	Trp	Asp	Gln	His	Tyr	Leu	Ser	Trp	
			340					345					350		•	
Ser M	let	Leu	Leu	G1 y	Val	Gly	Phe	Pro	Pro	Val	Asp	Gly	Leu	Ser	Pro	
		355	-	•			360					365				
Leu V	/al	Leu	Gly	Ile	Met	Ala	Val	Ala	Leu	Gly	Ala	Pro	Gly	Leu	Met	
3	370		. *			375					380			٠		
Leu l	Leu	Gly	Gly	Gly	Leu	Val	Leu	Leu	Leu	His	His	Lys	Lys	Tyr	Ser	
385					390					395	•				400	
Glu 1	Гуr	Gln	Ser	Ile	Asn				٠					:		
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1			٠.	• {	, ·	. •			10)	. •			15	5	
Pro	Arg	, Ar	g Se	r Phe	Phe	e Glo	u Sei	r Phe	e Ile	e Ar	g Thi	r Lei	ı Ile	e Ile	e Thr	

			20					25					30		
Cys	Val	Ala	Leu	Ala	Val	Val	Leu	Ser	Ser	Val	Ser	Ile	Cys	Asp	Gly
		35	21	~	. •		40					45			
His	Trp	Leu	Leu	Aļa	Glu	Asp	Arg	Leu	Phe	Gly	Leu	Trp	His	Phe	Cys
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Thr	Thr	Thr	Asn	Gln	Ser	Val	Pro	Ile	Cys	Phe	Arg	Asp	Leu	Gly	G1n
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Ala	His	Val	Pro	Gly	Leu	Ala	Val	Gly	Met	Gly	Leu	Val	Arg	Ser	Val
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Gly	Ala	Leu	Ala	Val	Val	Ala	Ala	Ile	Phe	Gly	Leu	Glu	Phe	Leu	Met
			100					105					110	,	
Val	Ser	Gln	Leu	Cys	Glu	Asp	Lys	His	Ser	Gln	Cys	Lys	Trp	Val	Met
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Gly	Ser	Ile	Leu	Leu	Leu	Val	Ser	Phe	Val	Leu	Ser	Ser	Gly	Gly	Leu
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Leu	Gly	Phe	Val	Ile	Leu	Leu	Arg	Asn	Gln	Val	Thr	Leu	Ile	Gly	Phe
145					150					155					160
Thr	Leu	Met	Phe	Trp	Cys	Glu	Phe	Thr	Ala	Ser	Phe	Leu	Leu	Phe	Leu
				165					170					175	
Asn	Ala	Ile	Ser	Gly	Leu	His	Ile	Asn	Ser	Ile	Thr	His	Pro	Trp	G1u
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	sapiens

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	Glu															
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	Phe															
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	cgg	•														001
Arg	Arg	Ala		Arg	Arg	Arg	116		Lys	Arg	GIA	WIR			Cys	
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Asn	Ala	Ile	Arg	His	Phe	Glu	Asn	Thr	Phe	Val	Val	Glu	Thr	Leu	Ile	
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Cys	Gly	Val	Val													
	265														••	
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gac	gcgt	ttc	tata	gagg	tg a	catg	tctc	t cc	attc	ctct	сса	accc	tgc	ccac	ctccct	1050
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Leu	Ala	Leu	Leu	Thr	Cys	Ser	Leu	Trp	Pro	Ala	Arg	Ala	Asp	Asn	Ala	
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Phe	Phe	Val	Pro	Pro	Asn	Ile	Lys	Gln	Trp	Ile	Ala	Leu	Leu	Gln	Arg	
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Ser	Arg	Gly	Ser	Leu	Val	Phe	Val	Ser	Ile	Ser	Phe	Ile	Val	Leu	Met	
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aag	aaa	gcc	atc	agt	aaa	ttg	aca	acc	agg	aca	gta	aag	aag	ggt	gac ·	766
Lys	Lys	Ala	Ile	Ser	Lys	Leu	Thr	Thr	Arg	Thr	Val	Lys	Lys	Gly	Asp	
•	· 240					245	٠				250				41 1 +	
aag	gaa	act	gac	cca	gac	ttt	gat	cat	tgt	gca	gtc	tgc	ata	gag	agc	814
Lys	Glu	Thr	Asp	Pro	Asp	Phe	Asp	His	Cys	Ala	Val	Cys	Ile	Glu	Ser	
255	٠.	٠.		-	260		•• :			265	1 τ	. :	\$. .	.r .	· 270· ·	
tat	aag	cag	aat	gat	gtc	gtc	cga	att	ctc	ccc	tgo	aag	cat	gtt	ttc	862

Tyr	Lys	Gln	Asn	Asp	Val	Val	Arg	Ile	Leu	Pro	Cys	Lys	His	Val	Phe	
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Gln	Ala	Val	Asn	Arg	Arg	Ser	Ala	Leu	Gly	Asp	Leu	Ala	Gly	Asp	Asn	
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Ser	Leu	Gly	Leu	Glu	Pro	Leu	Arg	Thr	Ser	Gly	Ile	Ser	Pro	Leu	Pro	
•	• •	٠.		355		• •		^.	360					365	-	
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5 ~	٠, ٠	385	. :	, -			390	. •				395	- 1	•		
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RNSDOCID -- WO - MITSEENAS I

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Met Arg Gly Ala Asn Ala Trp Ala
\mathbf{r}_{i} and \mathbf{r}_{i} and \mathbf{r}_{i} and \mathbf{r}_{i} and \mathbf{r}_{i} and \mathbf{r}_{i}
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Pro Leu Cys Leu Leu Leu Ala Ala Ala Thr Gln Leu Ser Arg Gln Gln
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BNSOCCID AWO 0112660A2 I

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Arg	Phe	Cys	Gly	Thr	Phe	Arg	Pro	Gly	Ala	Leu	Val	Ser	Ser	G1;	y Asn	
105		-			110	ı			٠	115					120	
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Phe	Met	t Ala	a Me	t Phe	e Sei	r Ala	a Ala	a Glu	ı Pro	Asr	ı Gl	u Ar	g Gl	y As	p Gln	
••		# F	14	0	. .	, .	- :	14	5				.15	0	· -,·	
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DNSDOOID - WO 0112880A2 L

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Asn	Trp	Pro	Asp	Arg	Asp	Tyr	Pro	Ala	Gly	Val	Thr	Cys	Val	Trp	His	
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Туŕ	Ile	Phe	Arg	Pro	Lys	Lys	Leu	Pro	Thr	Thr	Thr	Glu	Gln	Pro	Val	
265					270	٠, ,				275			•	;	280	
acc	acc	aca	ttc	cct	gta	acc	acg	ggt	tta	888	acc	acc ⁻	gtg	gcc	ttg	1097
Thr	Thr	Thr	Phe	Pro	Val	Thr	Thr	Gl v ·	Len	ive	Thr	Thr	Va 1	Alá	ום ו	

•			:	285					290					295	٠,	
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Ile I	le M	et	Gly	Gln	Val	Gly	Glu	Asp	Gly	Arg	Gly	Lys	·Ile	e Met	Pro	
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Asn S	er P	he	Ile	Met	Met	Phe	Lys	Thr	Lys	s Ası	ı Glı	n Lys	s Lei	ı Lei	ı Asp	
	; 3	95					400)				40	5			
gcc t	ta a	aa	aat	aag	g caa	a tgt	taa	acag	tgaa	ctg	tgtc	cat	ttaa	gc		1480
Ala I	.eu [.ys	Asn	Lys	s Glı	n Cys	3 .		-	. · ·	٠			٠.		
3 4	110			٠.		415	5 .			-		,	· · ·		4.7 * + 4.5	

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Met Leu Gln	
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Thr Leu Tyr Asp Tyr Phe Trp Trp Glu Arg Leu Trp Leu Pro Val Asn	

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Leu Thr Trp	Ala Asp	Leu Glu	Asp Arg	Asp Gly	Arg Va	l Tyr Ala	Lys	
20 ,		25 .		30		• 1	35	
gcc tca gat	ctc tat	atc acg	ctg ccc	ctg gcc	ttg ct	c ttc ctc	atc 3	77
Ala Ser Asp	Leu Tyr	Ile Thr	Leu Pro	Leu Ala	Leu Le	u Phe Leu	Ile	
	. 40	١		45		50		
gtt cga tac	ttc ttt	gag ctg	tac gtg	gct aca	cca ct	g gct gcc	ctc 4	25
Val Arg Tyr	Phe Phe	Glu Leu	Tyr Val	Ala Thr	Pro Le	ı Ala Ala	Leu	
	55		60			65		
ttg aac ata	aag gag	aaa act	cgg ctg	cgg gca	cct ccc	aac gcc	acc 47	73
Leu Asn Ile	Lys Glu	Lys Thr	Arg Leu	Arg Ala	Pro Pro	Asn Ala	Thr	
70	-		75		80)		
ttg gaa cat	ttc tac	ctg acc	agt ggc	aag cag	ccc aag	g cag gtg	gaa 52	21
Leu Glu His	Phe Tyr	Leu Thr	Ser Gly	Lys Gln	Pro Lys	Gln Val	Glu	
85		90			95			
gta gag ctt	ttg tcc	cgg cag	agc ggg	ctc tct	ggc cgc	cag gta	gag 56	39
Val Glu Leu	Leu Ser	Arg Gln	Ser Gly	Leu Ser	Gly Arg	Gln Val	Glu	
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cgt tgg ttc	cgt cgc	cgc cgc	aac cag	gac cgg	ccc agt	ctc ctc	aag 61	17
Arg Trp Phe	Arg Arg	Arg Arg	Asn Gln	Asp Arg	Pro Ser	Leu Leu	Lys	
71.1. · · · ·	120	· .		125		_ 130	• 5.	
aag; ttc.cga	gaa gcc	agc. tgg	aga ttc	aca ttt	tac ctg	att gcc	ttc 66	3 5
Lys Phe Arg	Glu Ala	Ser Trp	Arg Phe	Thr Phe	Tyr Leu	Ile Ala	Phe	
3.4 175 9	135	و بر دو في	140		, .	145	* •	

att	gcc	ggc	atg	gcc`	gtc	att	gtg	gat	aaa	ccc	tgg	ttc	tat	gac	atg	713
Ile	Ala	Gly	Met	Ala	Val	Ile	Val	Asp	Lys	Pro	Trp	Phe	Tyr	Asp	Met	
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Lys	Lys	Val	Trp	Glu	Gly	Tyr	Pro	Ile	Gln	Ser	Thr	Ile	Pro	Ser	Gln ·	
	165					170					175				٠	
tat	tgg	tac	tac	atg	att	gaa	ctt	tcc	ttc	tac	tgg	tcc	ctg	ctc	ttc	809
Tyr	Trp	Tyr	Tyr	Met	Ile	G1u	Leu	Ser	Phe	Tyr	Trp	Ser	Leu	Leu	Phe	
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agc	att	gcc	tct	gat	gtc	aag	cga	aag	gat	ttc	aag	gaa	cag	atc	atc	857
Ser	Ile	Ala	Ser	Asp	Val	Lys	Arg	Lys	Asp	Phe	Lys	Glu	Gln	Ile	Ile	
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cac	cat	gtg	gcc	acc	atc	att	ctc	atc	agc	ttt	tcc	tgg	ttt	gco	aat	905
His	His	Val	Ala	Thr	Ile	Ile	Leu	Ile	Ser	Phe	Ser	Trp	Phe	Ala	Asn	
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Tyr	· Ile	· Arı	g Ala	Gly	Thr	Leu	Ile	e Met	. Ala	Leu	ı His	s Asp	Se1	r Sei	r Asp	
		23	0				235	5				240)			
tac	cte	g ct	g gag	tca	gco	aag	ate	g ttt	taad	tac	c gc	g gg	a tg	g aa	g aac	1001
Tyj	r Lei	ı Le	u Glı	ı Ser	Ala	a Lys	Met	t Phe	e Asr	n Ty	r Ala	a Gl	y · Tr	p Ly	s Asn	. *
	24	5 '				250)	•			25	5		•		
ac	c tg	с аа	c aa	ato	c tte	e ato	gte	c tte	c gc	c at	t gt	t tt	t at	c at	c acc	1049
Th	г Су	s As	n Ası	n Il	e Ph	e Ile	e Va	1 Ph	e Ala	a Il	e Va	1 Ph	e Il	e Il	e Thr	• ,
26	0				26	5	. •		, ·	27	0 · ·		•	٠.	275	5
cg	a ct	g gt	c at	c ct	g cc	c tte	c tg	g at	c ct	g ca	t tg	c ac	c ct	g gt	g tac	1097

Arg	Leu	Val	Ile	Leu	Pro	Phe	Trp	Ile	Leu	His	Cys	Thr	Leu	Val	Tyr	
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cca	ctg	gag	ctc	·tat	cct	gcc	ttc	ttt	ggc	tat	tac	ttc	ttc	aat	tcc	1145
Pro	Leu	Glu	Leu	Tyr	Pro	Ala	Phe	Phe	Gly	Tyr	Tyr	Phe	Phe	Asn	Ser	
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Met 1	Met	Gly	Val	Leu	Gln	Leu	Leu	His	Ile	Phe	Trp	Ala	Tyr	Leu	Ile	
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Arg S	Ser	Asp	Arg	Glu	Glu	Thr	Glu	Ser	Ser	Glu	Gly	Glu	Glu	Ala	Ala	
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Ala (Gly	Gly	Gly	Ala	Lys	Ser	Arg	Pro	Leu	Ala	Asn	Gly	His	Pro	Ile	
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Leu A	Asn	Asn	Asn	His	Arg	Lys	Asn	Asp		•						-
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gatta	aatg	ca t	aaag	ccaa	g ga	acta	ccct	gct	ccct	gcg	ctat	aggg	tc a	cttt	aagct	1450
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gcttt	ttga	gg c	cctc	cctc	a go	tctc	tgtg	ggt	aggg	gtt	acaa	ttca	ca t	tcct	tattc	1690

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agcgtcgcc atg gtc tgc agg gag cag tta tca aag aat cag gtc aag 168
Met Val Cys Arg Glu Gln Leu Ser Lys Asn Gln Val Lys

tgg gtg ttt gcc ggc att acc tgt gtg tct gtg gtg gtc att gcc gca 216

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Cys	Ser	Pro	Asp	Ala	Asp	Met	Leu	Asp	Tyr	Leu	Leu	Ser	Leu	Gly	Gln	
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Ser	Lys	Lys	Ala	Met	Thr	Ala	Ala	Leu	Asn	Ser	Asn	Ile	Thr	Val	Leu	
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Glu	Ala	Asp	Val	Asn	Val	Glu	Gly	Leu	Gly	Thr	Ala	Asn	Glu	Thr	Gly	
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gtt	ccc	atc	atg	gca	cac	ccc	ccc	act	atc	tac	agt	gac	aac	aca	ctg	504
Val	Pro	Ile	Met	Ala	His	Pro	Pro	Thr	Ile	Tyr	Ser	Asp	Asn	Thr	Leu	
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Glu	Gln	Trp	Leu	Asp	Ala	Val	Leu	Gly	Ser	Ser	Gln	Lys	G1y	Ile	Lys	
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ctg	gac	ttc	aag	aac	atc	aag	gca	gtg	ggc	ccc	tcc	ctg	gac	ctc	ctg	. 600
Leu	Asp	Phe	Lys	Asn	Ile	Lys	Ala	Val	Gly	Pro	Ser	Leu	Asp	Leu	Leu	

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cgg	cag	ctg	aca	gag	gaa	ggc	aaa	gtc	cgg	cgg	ccc	ata	tgg	atc	aac	648
Arg	Gln	Leu	Thr	Glu	Glu	Gly	Lys	Val	Arg	Arg	Pro	Ile	Trp	Ile	Asn	
	ı	160	•				165					170				
gct	gac	atc	tta	aag	ggc	ccc	aac	atg	ctc	atc	tca	act	gag	gtc	aat	696
Ala	Asp	Ile	Leu	Lys	Gly	Pro	Asn	Met	Leu	Ile	Ser	Thr	Glu	Val	Asn	
	175					180				•	185	÷· ,				
gcc	aca	cag	ttc	ctg	gcc	ctg	gtc	cag	gag	aag	tat	ccc	aag	gct	acc	744
Ala	Thr	Gln	Phe	Leu	Ala	Leu	Val	Gln	Glu	Lys	Tyr	Pro	Lys	Ala	Thr	
190					195					200				-	205	· ••
cta	tct	cca	ggc	tgg	acc	acc	ttc	tac	atg	tcc	acg	tcc	сса	aac	agg	792
Leu	Ser	Pro	Gly	Trp	Thr	Thr	Phe	Tyr	Met	Ser	Thr	Ser	Pro	Asn	Arg	
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acg	tac	acc	caa	gcc	atg	gtg	gag	aag	atg	cac	gag	ctg	gtg	gga	gga	840
Thr	Tyr	Thr	Gln	Ala	Met	Val	G1u	Lys	Met	His	Glu	Leu	Val	Gly	Gly	. •
	•.	٠.	225					230					235			
gtg	ccc	cag	agg	gtc	acc	ttc	cct	gta	cgg	tct	tcc	atg	gtg	cgg	gct	888
Val	Pro	Gln	Arg	Val	Thr	Phe	Pro	Val	Arg	Ser	Ser	Met	Val	Arg	Ala	
*		240				•	245				•	250				
gcc	tgg	ссс	cac	ttc	agc	tgg	ctg	ctg	agc	caa	tct	gag	agg	tac	agc	936
Ala	Trp	Pro	His	Phe	Ser	Trp	Leu	Leu	Ser	Gln	Ser	Glu	Arg	Tyr	Ser	
	255			•		260		•			265				- •	
ctg	acg	ctg	tgg	cag	gct	gcc	tcg	gac	ccc	atg	tcg	gtg	gaa	gat	ctg	984
Leu	Thr	Leu	Trp	Gln	Ala	Ala	Ser	Asp	Pro	Met	Ser	Val	Glu	Asp	Leu '	
															285	

Leu Tyr Val Arg Asp Asn Thr Ala Val His Gln Val Tyr Tyr Asp Ile 290 295 300 ttt gag cct ctc ctg tca cag ttc aag cag ctg gcc ttg aat gcc aca Phe Glu Pro Leu Leu Ser Gln Phe Lys Gln Leu Ala Leu Asn Ala Thr 305 310 315 cgg aaa cca atg tac tac aca gga ggc agc ctg atc cct ctt ctc cag Arg Lys Pro Met Tyr Tyr Thr Gly Gly Ser Leu Ile Pro Leu Leu Gln 320 325 330 ctg cct ggg gat gac ggt ctg aat gtg gag tgg ctg gtt cct gac gtc Leu Pro Gly Asp Asp Gly Leu Asn Val Glu Trp Leu Val Pro Asp Val 335 340 345 cag ggc agc ggt aaa aca gca aca atg acc ctc cca gac aca gaa ggc Gln Gly Ser Gly Lys Thr Ala Thr Met Thr Leu Pro Asp Thr Glu Gly	1080 1128
290 295 300 ttt gag cct ctc ctg tca cag ttc aag cag ctg gcc ttg aat gcc aca Phe Glu Pro Leu Leu Ser Gln Phe Lys Gln Leu Ala Leu Asn Ala Thr 305 310 315 cgg aaa cca atg tac tac aca gga ggc agc ctg atc cct ctt ctc cag Arg Lys Pro Met Tyr Tyr Thr Gly Gly Ser Leu Ile Pro Leu Leu Gln 320 325 330 ctg cct ggg gat gac ggt ctg aat gtg gag tgg ctg gtt cct gac gtc Leu Pro Gly Asp Asp Gly Leu Asn Val Glu Trp Leu Val Pro Asp Val 335 340 345 cag ggc agc ggt aaa aca gca aca atg acc ctc cca gac aca gaa ggc	1128
Phe Glu Pro Leu Leu Ser Gln Phe Lys Gln Leu Ala Leu Asn Ala Thr 305 310 315 cgg aaa cca atg tac tac aca gga ggc agc ctg atc cct ctt ctc cag Arg Lys Pro Met Tyr Tyr Thr Gly Gly Ser Leu Ile Pro Leu Leu Gln 320 325 330 ctg cct ggg gat gac ggt ctg aat gtg gag tgg ctg gtt cct gac gtc Leu Pro Gly Asp Asp Gly Leu Asn Val Glu Trp Leu Val Pro Asp Val 335 340 345 cag ggc agc ggt aaa aca gca aca atg acc ctc cca gac aca gaa ggc	1128
Phe Glu Pro Leu Leu Ser Gln Phe Lys Gln Leu Ala Leu Asn Ala Thr 305 310 315 3	
cgg aaa cca atg tac tac aca gga ggc agc ctg atc cct ctt ctc cag Arg Lys Pro Met Tyr Tyr Thr Gly Gly Ser Leu Ile Pro Leu Leu Gln 320 325 325 330 ctg cct ggg gat gac ggt ctg gat gag ggg ggg ggg ggg ggg ggg ggg g	
Arg Lys Pro Met Tyr Tyr Thr Gly Gly Ser Leu Ile Pro Leu Leu Gln 320	
Arg Lys Pro Met Tyr Tyr Thr Gly Gly Ser Leu Ile Pro Leu Leu Gln 320	1176
320 325 330 ctg cct ggg gat gac ggt ctg aat gtg gag tgg ctg gtt cct gac gtc Leu Pro Gly Asp Asp Gly Leu Asn Val Glu Trp Leu Val Pro Asp Val 335 340 345 cag ggc agc ggt aaa aca gca aca atg acc ctc cca gac aca gaa ggc	1176
Leu Pro Gly Asp Asp Gly Leu Asn Val Glu Trp Leu Val Pro Asp Val 335 340 345 cag ggc agc ggt aaa aca gca aca atg acc ctc cca gac aca gaa ggc	1176
Leu Pro Gly Asp Asp Gly Leu Asn Val Glu Trp Leu Val Pro Asp Val 335 340 345 cag ggc agc ggt aaa aca gca aca atg acc ctc cca gac aca gaa ggc	1176
335 340 345 cag ggc agc ggt aaa aca gca aca atg acc ctc cca gac aca gaa ggc	
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Met Ile Leu Leu Asn Thr Gly Leu Glu Gly Thr Val Ala Glu Asn Pro	
370 375 380	
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Val Pro Ile Val His Thr Pro Ser Gly Asn Ile Leu Thr Leu Glu Ser	
tgc ctg cag cag ctg gcc aca cat ccc gga cac tgg ggc atc cat ttg	1368
Cys Leu Gln Gln Leu Ala Thr His Pro Gly His Trp Gly Ile His Leu	
400 405 410	
caa ata gcg gag ccc gca gcc ctc cgg cca tcc ctg gcc ttg ctg gca	

Gln	Ile	Ala	Glu	Pro	Ala	Ala	Leu	Arg	Pro	Ser	Leu	Ala	Leu	Leu	Ala	
	415	•				420	· · ·				425	• •		. •		
cgc	ctc	tcc	agc	ctt	ggc	ctc	ttg	cat	tgg	cct	gtg	tgg	gtt	ggg	gcc	1464
Arg	Leu	Ser	Ser	Leu	Gly	Leu	Ļeu	His	Trp	Pro	Val	Trp	Val	Gly	Ala	
430	•				435					440	. ,	.	٠	 ·	~445	
aaa	atc	tcc	cac	ggg	agt	ttt	tcg	gtc	ccc	ggc	cat	gtg	gct	ggc	aga	1512
Lys	Ile	Ser	His	Gly	Ser	Phe	Ser	Val	Pro	Gly	His	Val	Ala	Gly	Arg	
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Glu	Leu	Leu	Thr	Ala	Val	Ala	Glu	Val	Phe	Pro	His	Val	Thr	Val	Ala	÷
•	٠		465					470					475			
cca	ggc	tgg	cct	gag	gag	gtg	ctg	ggc	agt	ggc	tac	agg	gaa	cag	ctg	1608
Pro	Gly	Trp	Pro	Glu	Glu	Val	Leu	Gly	Ser	Gly	Tyr	Arg	Glu	Gln	Leu	
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Leu	Thr	Asp	Met	Leu	Glu	Leu	Cys	Gln	Gly	Leu	Trp	Gln	Pro	Val	Ser	
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Phe	Gln	Met	Gln	Ala	Met	Leu	Leu	Gly	His	Ser	Thr	Ala	Gly	Ala	lle	
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Gly	Arg	Leu	Leu	Ala				Arg								
•		•	•	530					535		•			540	. 4	
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ÁSP	Dwa	410	C1 _w	C1v	Acn	Tur	۸1a	Sar	Va1	Ara	Thr	Ala	Lau	ررغ ا	`Ala	

545	550	555	
gct agg gct gtg gac agg acc c	ga gtc tac tac	agg cta ccc cag ggc	1848
Ala Arg Ala Val Asp Arg Thr A	rg Val Tyr Tyr	Arg Leu Pro Gln Gly	
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Tyr His Lys Asp Leu Leu Ala H	is Val Gly Arg	Asn	
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St. 2	5	10	
cct ttc tcc ttc ctg ctg cta.	gtg ctg ctg	gtg acg cgg agc ccg	218
Pro Phe Ser Phe Leu Leu Leu	Val Leu Leu Leu	Val. Thr Arg Ser Pro	•

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Val	Asn	Åla	Cys	Leu	Leu	Thr	Gly	Ser	Leu	Phe	Vail	Leu	Leu	Arg	Val	
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Pro	Arg	Asp	Arg	Ile	Ser	Ala	Ile	Ala	His	Arg	Gly	Gly	Ser	His	Asp	
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Ala	Pro	Glu	Asn	Thr	Leu	Ala	Ala	Ile	Arg	Gln	Ala	Ala	Lys	Asr	Gly	
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Ala	Thr	Gly	Val	Glu	Leu	Asp	Ile	Glu	Phe	Thr	Ser	. Ası	Gly	y I16	Pro	
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gto	tta	atg	cac	gat	aac	aca	gta	gat	: agg	g ace	g act	t ga	t gg	g ac	t ggg	506
Val	. Le	ı Met	His	. Asp	Asn	Thr	· Val	Asp	Arg	g Thr	Th	r As	p G1:	y Th	r · Gly	
•	110) [']	. '		•	115	5.		•		12	0	•		· i.	
cġ	a tt	g tgi	gat	t tte	g aca	a tti	t gaa	a caa	a ati	t agg	g aa	g ct	g aa	t cc	t gca	554
Ar	g Le	u Cys	s Ası	p Lei	ı Thi	r Phe	e Glu	u Gli	n·Ile	e Ar	g Ly	s Le	u As	n·Pr	o Ala	
12	5		,	٠,	130	0			- '	13	5	`			140	
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A1	a As	n Hi	s Ar	g Le	u Ar	g As	n As	p Ph	e Pr	o As	p Gl	u Ly	s Il	e Pr	o Thr	
	٠		• .	14	5	٠.		٠.	· 15	0 -		`- -	• •	15	55	:

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Leu	Arg	Glu	Ala	Val	Ala	Glu	Cys	Leu	Asn	His	Asn	Leu	Thṛ	Ile	Phe	-
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Phe	Asp	Val	Lys	Gly	His	Ala	His	Lys	Ala	Thr	Glu	Ala	Leu	Lys	Lys	
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Met	Tyr	Met	Glu	Phe	Pro	Gln	Leu	Tyr	Asn	Asn	Ser	Val	Val	Cys	Ser	
	190					195					200					
ttc	ttg	cca	gaa	gtt	atc	tac	aag	atg	aga	caa	aca	gat	cgg	gat	gta	794
Phe	Leu	Pro	Glu	Val	Ile	Tyr	Lys	Met	Arg	Gln	Thr	Asp	Arg	Asp	Val	
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Ile	Thr	Ala	Leu	Thr	His	Arg	Pro	Trp	Ser	Leu	Ser	His	Thr	Gly	Asp	
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Met	Asp	Ile	Leu	Leu	Asp	Trp	Ser	Met	His	Asn	Ile	Leu	Trp	Tyr	Leu	
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Cys	Gly	Ile	Ser	Ala	Phe	Leu	Met	Gln	Lys	Asp	Phe	Val	Ser	Pro _.	Ala	
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tac	ttg	aag	aag	tgg	tca	gct	aaa	gga	atc	cag	gtt	gtt	ggt	tgg	act	1034

Tyr Leu Lys Lys Trp Ser Ala Lys Gly Ile Gln Val Val Gly Trp Thr	
285 290 295 300	
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Val Asn Thr Phe Asp Glu Lys Ser Tyr Tyr Glu Ser His Leu Gly Ser	
305 310	
age tat ate act gae age atg gta gaa gae tge gaa eet cae tte	1127
Ser Tyr Ile Thr Asp Ser Met Val Glu Asp Cys Glu Pro His Phe	
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Met Ser Pro Glu Glu Trp Thr Tyr Leu Val Val Leu Leu Ile	
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Ser Ile Pro Ile Gly Phe Leu Phe Lys Lys Ala Gly Pro Gly Leu Lys	
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Arg Trp Gly Ala Ala Ala Val Gly Leu Gly Leu Thr Leu Phe Thr Cys	
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Gly Pro His Thr Leu His Ser Leu Val Thr Ile Leu Gly Thr Trp Ala	
55 60	
ctc att cag gcc cag ccc tgc tcc tgc cac gcc ctg gct ctg gcc tgg	480
Leu Ile Gln Ala Gln Pro Cys Ser Cys His Ala Leu Ala Leu Ala Trp	
65 70 75	
act ttc tcc tat ctc ctg ttc ttc cga gcc ctc agc ctc ctg ggc ctg	528
Thr Phe Ser Tyr Leu Leu Phe Phe Arg Ala Leu Ser Leu Leu Gly Leu	
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ccc act ccc acg ccc ttc acc aat gcc gtc cag ctg ctg acg ctg	576
Pro Thr Pro Thr Pro Phe Thr Asn Ala Val Gln Leu Leu Thr Leu	

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Lys	Leu	Val	Ser	Leu	Ala	Ser	Glu	Val	Gln	Asp	Leu	His	Leu	Ala	G1n	
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Arg	Lys	Glu	Met	Ala	Ser	Gly	Phe	Ser	Lys	Gly	Pro	Thr	Leu	Gly	Leu	
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Leu	Pro	Asp	Val	Pro	Ser	Leu	Met	Glu	Thr	Leu	Ser	Tyr	Ser	Tyr	Cys:	
		145					150					155				į
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Tyr	Val	Gly	Ile	Met	Thr	Gly	Pro	Phe	Phe	Arg	Tyr	Arg	Thr	Tyr	Leu	
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Asp	Trp	Leu	Glu	Gln	Pro	Phe	Pro	Gly	Ala	Val	Pro	Ser	Leu	Arg	Pro	
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Leu	Leu	Arg	Arg	Ala	Trp	Pro	Ala	Pro	Leu	Phe	Gly	Leu	Leu	Phe	Leu	
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ctc	tcc	tct	cac	ctc	ttc	ccg	ctg	gag	gcc	gtg	cgc	gag	gac	gcc	ttc	91
Leu	Ser	Ser	His	Leu	Phe	Pro	Leu	Glu	Ala	Val	Arg	Glu	∵ A sp	Ala	Phe	
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Tyr	Ala	Arg	Pro	Leu	Pro	Ala	Arg	Leu	Phe	Tyr	Met	Ile	Pro	Val	· Phe-	
٦.		225				: . :	230	,	٠.		: .	235	; .	,	ይል ዕንኳ	

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Phe Ala Phe Arg Met Arg	Phe Tyr Val Ala Trp	Ile Ala Ala Glu Cys	
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ggc tgc att gcc gcc ggc	ttt ggg gcc tac ccc	gtg gcc gcc aaa gcc	1056
Gly Cys Ile Ala Ala Gly	Phe Gly Ala Tyr Pro	Val Ala Ala Lys Ala	
255 260	265	270	
cgg gcc gga ggc ggc ccc	acc ctc caa tgc cca	ccc ccc agc agt ccg	1104
Arg Ala Gly Gly Gly Pro	Thr Leu Gln Cys Pro	Pro Pro Ser Ser Pro	
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Glu Lys Ala Ala Ser Leu	Glu Tyr Asp Tyr Glu	Thr Ile Arg Asn Ile	
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Asp Cys Tyr Ser Thr Asp	Phe Cys Val Arg Val	Arg Asp Gly Met Arg	
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Tyr Trp Asn Met Thr Val	Gln Trp Trp Leu Ala	Gln Tyr Ile Tyr Lys	
320	325	330	
age gea cet gee egt tee	tat gtc ctg cgc ctt	tagaagcaga aactcagcc	1300
Ser Ala Pro Ala Arg Ser	Tyr Val Leu Arg Leu	• • .	
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ENSPOCID - WC - DI IOCCOAO I

60

58 / 307

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atg	ggcc	tcc	ccat	gtgg	at c	ctta	gţgc	t gt	ggca	gagc	cct	tgtt	att :	gtgc	tgggat	240
ttte	cct	cca ˈ	gctc	ccgg	cc g	gaage	ctgg	g ct	cacg	tggg	agc	tcag	tgc	cctc	ctgcta	300
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Cys	Thr	Phe	Leu	Val	Leu	Ala	Ile	Thr	Arg	His	Gln	Ser	Leu	Thr	Asp	
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Pro	Thr	Ser	Tyr	Tyr	Leu	Ser	Ser	Val	Trp	Ser	Phe	Ile	Ser	Phe	Lys	
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Trp	Ala	Phe	Leu	Leu	Ser	Leu	Tyr	Ala	His	Arg	Tyr	Arg	Ala	Asp	Phe	
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Trp Gly Trp Gly His Cys Ala Pro	Ser Pro Leu Leu	Leu Trp Thr Leu
10 15	20	
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Leu Leu Phe Ala Ala Pro Phe Gly	Leu Leu Gly Glu	Lys Thr Arg Gln
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Val Ser Leu Glu Val Ile Pro Asn	Trp Leu Gly Pro	Leu Gln Asn Leu
45	50	55
ctt cat ata cgg gca gtg ggc acc	aat tcc aca ctg	cac tat gtg tgg 245
Leu His Ile Arg Ala Val Gly Thr	Asn Ser Thr Leu	His Tyr Val Trp
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Ser Ser Leu Gly Pro Leu Ala Val	Val Met Val Ala	Thr Asn Thr Pro
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cac agc acc ctg agc gtc aac tgg	agc ctc ctg cta	tcc cct gag ccc 341
His Ser Thr Leu Ser Val Asn Trp	Ser Leu Leu Leu	Ser Pro Glu Pro
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Asp	Gly	Gly	Leu	Met	Val	Leu	Pro	Lys	Asp	Ser	Ile	Gln	Phe	Ser	Ser	
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Ala	Leu	Val	Phe	Thr	Arg	Leu	Leu	Glu	Phe	Asp	Ser	Thr	Asn	Val	Ser ·	
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Asp	Thr	Ala	Ala	Lys	Pro	Leu	Gly	Arg	Pro	Tyr	Pro	Pro	Tyr	Ser	Leu	
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gcc	gat	ttc	tct	tgg	aac	aac	atc	act	gat	tca	ttg	gat	cct	gcc	acc	533
Ala	Asp	Phe	Ser	Trp	Asn	Asn	Ile	Thr	Asp	Ser	Leu	Asp	Pro	Ala	Thr	
		155		•			160					165		.•		
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Phe	'Ala	Asn	Gly	Ser	Leu	Ala	Phe	Arg	Val	Gln	Ala	Phe	Ser	Arg	Ser 🕝	
185					190					195					200	
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Ser	Arg	Pro	Ala	Gln	Pro	Pro	Arg	Leu	Leu	His	Thr	Ala	Asp	Thr	Cys	
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Gln	Leu	Glu	Val	Ala	Leu	Ile	Gly	Ala	Ser	Pro	Arg	Gly	Asn	Arg	Ser	
		-	220	• •		•		225	<i>.</i> `		r .	•	230		J 15 1	
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Ser	Met	Gln	Glu	Gln	His	Ser	Ile	Asp	Asp	Glu	Tyr	Ala	Pro	Ala	Val	
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ttc	cag	ttg	gac	cag	cta	ctg	tgg	ggc	tcc	ctc	cca	tca	ggc	ttt	gca	869
Phe	Gln	Leu	Asp	Gln	Leu	Leu	Trp	Gly	Ser	Leu	Pro	Ser	Gly	Phe	Ala	
265	,	-			270					275	,				280	
cag	tgg	cga	cca	gtg	gct	tac	tcc	cag	aag	ccg	ggg	ggc	cga	gaa	tca	917
Gln	Trp	Arg	Pro	Val	Ala	Tyr	Ser	Gln	Lys	Pro	Gly	Gly	Arg	Glu	Ser	
			,	285					290					295		
gcc	ctg	ccć	tgc	caa	gct	tcc	cct	ctt	cat	cct	gcc	tta	gca	tac	tct	965
Ala	Leu	Pro	Cys	Gln	Ala	Ser	Pro	Leu	His	Pro	Ala	Leu	Ala	Tyr	Ser	
			300					305					310)		
ctt	ccc	cag	tca	ccc	att	gtc	cga	gcc	ttc	ttt	ggg	tcc	cag	aat	aac	1013
Leu	Pro	Gln	Ser	Pro	Ile	Val	Arg	Ala	Phe	Phe	Gly	Ser	G1r	n Asn	Asn.	
		315	i				320)				325	;	.•		
tto	tgt	gcc	ttc	aat	ctg	acg	ttc	ggg	gct	tcc	aca	ggo	cct	t ggo	tat	1061
Phe	Cys	s Ala	Phe	e Asn	Leu	Thr	Phe	Gly	Ala	Ser	Thr	Gly	Pro	o Gly	y Tyr	
	330)				335	;				340)				
tgg	g gad	c caa	a cad	tac	cto	ago	tgg	g tcg	g atg	g cto	cte	g ggt	t gt	g gg	c tực	1109
Trj	As ₁	Glr	n His	s Tyi	r Leu	ı Ser	Tr	Sez	r Met	t Le	u Lei	ı Gly	y Va	1 G1;	y Phe	
34	5 ~			. .	350)				35	5				360	
cc	t rcc	a gt	g ga	c gg	c ttg	g tco	c cca	a cta	a gto	c ct	g gg	c at	c at	g gc	a gtg	1157
															a Val	

365 370 375	
gcc ctg ggt gcc cca ggg ctc atg ctg cta ggg ggc ggc ttg gtt ctg	1205
Ala Leu Gly Ala Pro Gly Leu Met Leu Leu Gly Gly Gly Leu Val Leu	1
380 385 390	•
ctg ctg cac cac aag aag tac tca gag tac cag tcc ata aat taa	1250
Leu Leu His His Lys Lys Tyr Ser Glu Tyr Gln Ser Ile Asn	
395 400 405	
ggcccgctct ctggagggaa ggacattact gaacctgtct tgctgtgcct cgaaactc	etg 1310
gaggttggag catcaagttc cagccggccc cttcactccc ccatcttgct tttctgt	gga 1370
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cttcttgcat ctccacacat ttcccttgga tgggacttgc aggcctaaat gagaggc	att 1550
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⟨220⟩	*:•
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<222> (53) (631)	•
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acageegage agetggageg ategaggetg cagegggee geegggegea ge atg	55
Met'	<i>:</i>
· · · · · · · · · · · · · · · · · · ·	

BNSOCIO: <WO 0112660A2 I

act	gcc	gtc	ggc	gtg	cag	gcc	cag	agg	cct	ttg	ggc	caa	agg	cag	ccc	103
Thr	Ala	Val	Gly	Val	Gln	Ala	Gln	Arg	Pro	Leu	Gly	Gln	Arg	Gln	Pro	
			. 5			•		10					15			
cgc	cgg	tcc	ttc	ttt	gaa	tcc	ttc	atc	cgg	acc	ctc	atc	atc	acg	tgt	151
Arg	Arg	Ser	Phe	Phe	Glu	Ser	Phe	Ile	Arg	Thr	Leu	Ile	Ile	Thr	Cys	
		20					25					30				
gtg	gcc	ctg	gct	gtg	gtc	ctg	tcc	tcg	gtc	tcc	att	tgt	gat	ggg	cac	199
Val	Ala	Leu	Ala	Val	Val	Leu	Ser	Ser	Val	Ser	Ile	Cys	Asp	Gly	His	
	35					40					45					
tgg	ctc	ctg	gct	gag	gac	cgc	ctc	ttc	ggg	ctc	tgg	cac	ttc	tgc	acc	247
Trp	Leu	Leu	Ala	Glu	Asp	Arg	Leu	Phe	Gly	Leu	Trp	His	Phe	Cys	Thr	
50					55					60					65	
acc	acc	aac	cag	agt	gtg	ccg	atc	tgc	ttc	aga	gac	ctg	ggc	cag	gcc	295
Thr	Thr	Asn	Gln	Ser	Val	Pro	Ile	Cys	Phe	Arg	Asp	Leu	Gly	Gln	Ala	
				70					75					80		
cat	gtg	ccc	ggg	ctg	gcc	gtg	ggc	atg	ggc	ctg	gta	cgc	agc	gtg	ggc	343
His	Val	Pro	Gly	Leu	Ala	Val	Gly	Met	Gly	Leu	Val	Arg	Ser	Val	Gly	
			85					90					95			
gcc	ttg	gcc	gtg	gtg	gcc	gcc	att	ttt	ggc	ctg	gag	ttc	ctc	atg	gtg	391
Ala	Leu	Ala	Val	Val	Ala	Ala	Ile	Phe	Gly	Leu	Glu	Phe	Leu	Met	Val	
· •••		100		٠			105					110				
tcc	cag	ttg	tgc	gag	gac	aaa	cac	tca	cag	tgc	aag	tgg	gtc	atg	ggt.	439
Ser	Gln	Leu	Cys	Glu	Asp	Lys	His	Ser	Gln	Cys	Lys	Trp	Val	Met	Gly	
	-115		. •			120					125					
tcc	atc	ctc	ctc	ctg	gtg	tct	ttc	gtc	ctc	tcc	tcc	ggc	ggg	ctc	ctg	487

27

Ser	Ile	Leu	Leu	Leu	Val	Ser	Phe	Val	Leu	Ser	Ser	Gly	Gly	Leu	Leu	
130		•	•		135					140		•	•	•••	145	
ggt	ttt	gtg	atc	ctc	ctc	agg	aac	caa	gtc	aca	ctc	atc	ggc	ttc	acc	535
Gly	Phe	Val	Ile	Leu	Leu	Arg	Asn	Gln	Val	Thr	Leu	Ile	Gly	Phe	Thr	
		•1 -		150					155		·			160	ů.;	
cta	atg	ttt	tgg	tgc	gaa	ttc	act	gcc	tcc	ttc	ctc	ctc	ttc	ctg	aac	583
Leu	Met	Phe	Trp	Cys	Glu	Phe	Thr	Ala	Ser	Phe	Leu	Leu	Phe	Leu	Asn	
			165				. •	170	÷			٠.	175			
gcc	atc	agc	ggc	ctt	cac	atc	aac	agc	atc	acc	cat	ccc	tgg	gaa	tg	630
Ala	Ile	Ser	Gly	Leu	His	Ile	Asn	Ser	Ile	Thr	His	Pro	Trp	Glu	·	:-
		180					185					190				
acc	gtgg	aaa	tttt	aggc	cc c	ctcc	aggg	a ca	tcag	attc	cac	aaga	aaa	tatg	gtcaaa	690
atg	ggac	t t t	tcca	gcat	gt g	gcct	ctgg	t gg	ggct	gggt	tgg	acaa	ggg	cctt	gaaacg	750
gct	gcct	gtt	tgcc	gata	ac t	tgtg	ggtg	g to	agcc	agaa	atg	gccc	ggg	ggcc	tctgca	810
cct	ggto	tgc	aggg	ccag	ag g	ccag	gagg	g tg	cctc	agtg	сса	ccaa	ctg	caca	ggctta	870
gcc	agat	gtt	gatt	ttag	ag g	aaga	aaaa	a ac	attt	taaa	act	cctt	ctt	gaat	tttctt	930
ccc	tgga	ctg	gaat	acag	tt g	gaag	caca	g gg	gitaa	ctgg	tac	ctga	gct	agct	gcacag	990
cca	agga	tag	ttca	tgcc	tg t	ttca	ttga	c ac	gtgo	tggg	ata	gggg	gctg	caga	atccct	1050
888	gete	cca	gggt	tgtt	aa g	gaate	gato	a ti	tcttc	cago	taa	igggt	tcca	atca	gtgcct	1110
att	ctt	cac	cago	ctcaa	ag e	ggcct	tcgt	a te	gtatg	gtece	tgg	ctti	cagc	tttg	gtcatg	1170
cca	aaaga	aggc	agag	gttca	agg a	attco	ctca	ag aa	atgco	cctgo	aca	cagi	tagg	ttto	caaacc	1230
ati	ttga	ctcg	gtti	tgcct	tcc (ctgc	cgti	tg t	ttaaa	acctt	aca	aaac	cctg	gata	acccca	1290
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ggi	gttt	cctt	ccga	agaaı	gag	ttct	tgago	ca a	gctc	tecea	a gga	aggg	ccca	cct	gactgct	1410
90	taca		cct	occe.	aaσ i	ספפפי	otøt	σt ø	cato	tgto:	t gt	cttt	tgtg	agg	gttagac	1470

agc	ctca	388	cacc	attt	tt a	atco	cagaa	а са	catt	tcaa	aga	gcac	gta	tcta	gacct	g :	153
ctg	gacto	ctg	cagg	gggt	ga g	gggg	aacag	g cg	agag	cttg	ggt	aatg	att	aaca	cccat	g :	159
ctg	ggga1	tgc	atgg	aggt;	ga a	gggg	gccag	g ga	acca	gtgg	aga	tttc	cat	cctt	gccag	c :	165
acg	tctgi	tac	ttct	gttc	at t	aaag	tgcto	cc	tttc	tagt	cct	tt				1	169
	•																
<210)> 3 1	l															
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Gly	Pro	Thr	Asn	Ser	Thr	Thr	Arg	Pro	Pro	Ser	Thr	Pro	Glu	Gly	Ile		
			20					25					30				
Ala	Leu	Ala	Tyr	Gly	Ser	Leu	Leu	Leu	Met	Ala	Leu	Leu	Pro	Ile	Phe		
		35					40					45					
Phe	Gly	Ala	Leu	Arg	Ser	Val	Arg	Cys	Ala	Arg	Gly	Lys	Asn	Ala	Ser		
	· 50					55					60						
Asp	Met	Pro	Glu	Thr	Ile	Thr	Ser	Arg	Asp	Ala	Ala	Arg	Phe	Pro	Ile		
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Ile	Ala	Ser	Cys	Thr	Leu	Leu	Gly	Leu	Tyr	Leu	Phe	Phe	Lys	Ile	Phe		
٠,	į v			85				,	90				٠.	95			
Ser	Gln	Glu	Tyr	Ile	Asn	Leu	Leu	Leu	Ser-	Met	Tyr	Phe	Phe	Val	Leu		
,	. : .		100			• .		105			-		110				
Gly:	Ile	Leu	Ala	Leu	Ser	His	Thr	Ile	Ser	Pro	Phe	Met	Asn	Lys	Phe :		

BNSDOCID--WO 0112660A2 1 .

		115					120					125		٠.	٠.	-
Phe	Pro	Ala	Ser	Phe	Pro	Asn	Arg	Gln	Tyr	Gln	Leu	Leu	Phe	Thr	Gln	
	130					135	,				140		.,		.·	
Gly	Ser	Gly	Glu	Asn	Lys	Glu	Glu	Ile	Ile	Asn	Tyr	Glu	Phe	Asp	Thr	
145					150					155					160	
Lys	Asp	Leu	Val	Cys	Leu	Gly	Leu	Ser	Ser	Ile	Val	Gly	Val	Trp	Tyr	
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Leu	Leu	Arg	Lys	His	Trp	Ile	Ala	Asn	Asn	Leu	Phe	Gly	Leu	Ala	Phe	
			180					185					190		٠	
Ser	Leu	Asn	Gly	Val	Glu	Leu	Leu	His	Leu	Asn	Asn	Val	Ser	Thr	Gly	
		195					200			·		205		.*		
Cys	Ile	Leu	Leu	Gly	Gly	Leu	Phe	Ile	Tyr	Asp	Val	Phe	Trp	Val	Phe	;
	210					215					220					
Gly	Thr	Asn	Val	Met	Val	Thr	Val	Ala	Lys	Ser	Phe	Glu	Ala	Pro	Ile	;
225					230					235		•		:	240) .
Lys	Leu	Val	Phe	Pro	Gln	Asp	Leu	Leu	Glu	Lys	Gly	Leu	Glu	Ala	Asn	1
	<i>:</i> .	; .		245	,				250		,	•		255	; , : ,	
Asn	Phe	Ala	Met	Leu	Gly	Leu	Gly	Asp	Val	Val	Ile	Pro	Gly	Ile	Phe	?
		٠.	260					265					270)		
Ile	Ala	Lei	ı Leu	ı Leu	Arg	Phe	Asp	Ile	Ser	Leu	Lys	Lys	s Asr	1 Thu	. His	5
		275	5				280)				285	5			• •
Thi	Tyr	. Phe	e Tyr	Thi	Ser	Phe	Ala	Ala	Tyr	· Ile	Phe	G1;	y Let	ı Gl	/ Le	u
	290) ·				295	5 .	. •		.• •	300).	•:		r, * ·	٠;
Thi	r Ile	e Pho	e Ile	e Mei	t His	s Ile	e Phe	Lys	His	s Ala	a Gl	n Pro	o Ala	a Le	ı Le	u
309	5 :			<u>.</u>	310)		, - ·		-319	5 .		٠		- 32	0

Tyr	Leu	Val	Pro	Ala	Cys	Ile	Gly	Phe	Pro	Val	Leu	Val	Ala	Leu	Ala
				325					330					335	
Lys	Gly	Glu	Val	Thr	Glu	Met	Phe	Ser	Tyr	Glu	Glu	Ser	Asn	Pro	Lys
			340					345					350		, .
Asp	Pro	Ala	Ala	Val	Thr	Glu	Ser	Lys	Glu	Gly	Thr	Glu	Ala	Ser	Ala
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Ser	Lys	Gly	Leu	Glu	Lys	Lys	Glu	Lys							
	370					375								,	į
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<211	> 81	l													
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1			٠.	. 5					10					15	٠.
Trp	Gly	Leu	Val	Gly	Ile	Ala	Gly	Pro	Trp	Phe	Val	Pro	Lys	Gly	Pro
	,		20					25					30		
Asn	Arg	Gly	Val	Ile	Ile	Thr	Met	Leu	Val	Ala	Thr	Ala	Val	Cys	Cys
		- 35	• :			•	40					45			
Tyr	Leu	Phe	Trp	Leu	Ile	Ala	Ile	Leu	Ala	Gln	Leu	Asn	Pro	Leu	Phe
•	.50	• .		٠.	,	55					60			÷	٠
Gly	Pro	Gln	Leu	Lys	Asn	Glu	Thr	Ile	Trp	Tyr	Val	Arg	Phe	Leu	Trp
65)		, :		.70	٠.	÷	•		, 75		: .			80
Glu				•					•	•				:	7

2.			•				
<210> ⋅33 - ⋅		. •			.•	. • •	••••
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Gln Ser Gln	Glu Pro	Lys Thr	Thr Ser	Leu Gln	Lys Glu	Leu Gly	Leu
	20		25			30	
Ile Ser Gly	Ile Ser	lle Ile	Val Gly	Thr Ile	Ile Gly	Ser Gly	Ile ·
35			40		45	·.	· · · .
Phe Val Ser	Pro Lys	Ser Val	Leu Ser	Asn Thr	Glu Ala	Val Gly	Pro.
50	· • ,	- 55			60		-
Cys Leu Ile	Ile Trp	Ala Ala	Cys Gly	Val Leu	Ala Thr	Leu Gly	Ala
65	• 1	70		75	: .:.	***	80
Leu Cys Phe	Ala Glu	ı Leu Gly	Thr Met	Ile Thr	Lys Ser	Gly Gly	Glu
	88	5		90		-95	1.4%
Tyr Pro Tyr	Leu Met	t Glu Ala	Tyr Gly	Pro Ile	Pro Ala	Tyr Leu	Phe
	100		105	; ·		. 110 .	:
Ser Trp Ala	Ser Le	ı Ile Val	Ile Lys	Pro Thr	Ser Phe	Ala Ile	lle
<i>i</i>	5	14	120	٠.	. 125	; , , , · ·	
Cys Leu Se							
130		135	5		140		a_{i}

Lys	Pro	Pro	Gln	Ile	Val	Val	Lys	Cys	Leu	Ala	Ala	Ala	Ala	Ile	Leu
145					150					155					160
Phe	Ile	Ser	Thr	Val	Asn	Ser	Leu	Ser	Val	Arg	Leu	Gly	Ser	Tyr	Val
	: .	ſ		165					170					175	
Gln	Asn	Ile	Phe	Thr	Ala	Ala	Lys	Leu	Val	Ile	Val	Ala	Ile	Ile	Ile
			180					185					190		
Ile	Ser	Gly	Leu	Val	Leu	Leu	Ala	Gln	Gly	Asn	Thr	Lys	Asn	Phe	Asp
		195					200					205			
Asn	Ser	Phe	Glu	Gly	Ala	Gln	Leu	Ser	Val	Gly	Ala	Ile	Ser	Leu	Ala
	210					215					220				
Phe	Tyr	Asn	Gly	Leu	Trp	Ala	Tyr	Asp	Gly	Trp	Asn	Gln	Leu	Asn	Tyr
225	٠.		•		230					235					240
Ile	Thr	Glu	Glu	Leu	Arg	Asn	Pro	Tyr	Arg	Asn	Leu	Pro	Leu	Ala	Ile
				245					250					255	
Ile	Ile	Gly	Ile	Pro	Leu	Val	Thr	Ala	Cys	Tyr	Ile	Leu	Met	Asn	Val
		٠	260					265					270	:	
Ser	Tyr	Phe	Thr	Val	Met	Thr	Ala	Thr	Glu	Leu	Leu	Gln	Ser	Gln	Ala
		275					280					285			
Val	Ala	Val	Thr	Phe	Gly	Asp	Arg	Val	Leu	Tyr	Pro	Ala	Ser	Trp	Ile
	290					295					300				
Val	Pro	Leu	Phe	Val	Ala	Phe	Ser	Thr	Ile	Gly	Ala	Ala	Asn	Gly	Thr
305					310					315				٠ ٠.	320
Cys	Phe	Thr	Ala	Gly	Arg	Leu	Ile	Tyr	Val	Ala	Gly	Arg	Glu	Gly	His
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Met	Leu	Lys	Val	Leu	Ser	Tyr	Ile	Ser	Val	Arg	Arg	Leu	Thr	Pro	Ala

	340					345				٠	350		
Pro Ala Ile	Ile	Phe	Tyr	Gly	Ile	Ile	Ala	Thr	Ile	Tyr	Ile	Ile	Pro
355					360	<i>.</i> ·		÷ ė		365	•	•	
Gly Asp Ile	Asn	Ser	Leu	Val	Asn	Tyr	Phe	Ser	Phe	Ala	Ala	Trp	Leu
370		•	•	375	•		, •		380	•	•		
Phe Tyr Gly	Leu	Thr	Ile	Leu	Gly	Leu	Ile	Val	Met	Arg	Phe	Thr	Arg
385	÷		390	÷				395					400
Lys Glu Leu	Glu	Arg	Pro	Ile	Lys	Val	Pro	Val	Val	Ile	Pro	Val	Leu
		405					410					415	• •
Met Thr Leu	Ile	Ser	Val	Phe	Leu	Val	Leu	Ala	Pro	Ile	Ile	Ser	Lys
	420					425					430		٠.
Pro Thr Trr	Glu	Tyr	Leu	Tyr	Cys	Val	Leu	Phe	Ile	Leu	Ser	Gly	Leu
435	· · ·				440					445			
Leu Phe Tyr	Phe	Leu	Phe	Val	His	Tyr	Lys	Phe	Gly	Trp	Ala	Gln	Lys
450 -		٠		455	• •			-	460		-	•	
Ile Ser Lys	Pro	Ile	Thr	Met	His	Leu	Gln	Met	Leu	Met	Glu	Val	Val
465		:	470			• •		475			••		· 480 ··
Pro Pro Glu	ı Glu	Asp	Pro	Glu									
		485		4		٠.	٠.		•	•			V Car
													•
<210> 34	٠	•		•		• •	•		•	• • •	٠		
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<212> PRT	٠			· ·				··· ,	•	• . • .	., .		الاحدادي
<213> Homo	sap	iens								•			
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.1	' ; .			5					. 10			٠.		15	
Val	Ala	Ala	Ala	Ala	Phe	Ala	Ile	Asn	Gly	Leu	Ser	Tyr	Gly	Leu	Leu
		.••	20		٠.		٠	25					30		
Arg	Ser	Leu	Gly	Leu	Ala	Phe	Pro	Asp	Leu	Ala	Glu	His	Phe	Asp	Arg
		- 35					40					45			
Ser	Ala	Gln	Asp	Thr	Ala	Trp	Ile	Ser	Ala	Leu	Ala	Leu	Ala	Val	Gln
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Gln	Ala	Ala	Ser	Pro	Val	Gly	Ser	Ala	Leu	Ser	Thr	Arg	Trp	Gly	Ala
65					70					75					80
Arg	Pro	Val	Val	Met	Val	Gly	Gly	Val	Leu	Ala	Ser	Leu	Gly	Phe	Val
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Phe	Ser	Ala	Phe	Ala	Ser	Gly	Leu	Leu	His	Leu	Tyr	Leu	Gly	Leu	Gly
			100					105					110		
Leu	Leu	Ala	Gly	Phe	Gly	Trp	Ala	Leu	Val	Phe	Ala	Pro	Ala	Leu	Gly
	,	115					120					125			
Thr	Leu	Ser	Arg	Tyr	Phe	Ser	Arg	Arg	Arg	Val	Leu	Ala	Val	Gly	Leu
	130					135					140				
Ala	Leu	Thr	Gly	Asn	Gly	Ala	Ser	Ser	Leu	Leu	Leu	Ala	Pro	Ala	Leu
145	:	•			150					155		•			160
Gln	Leu	Leu	Leu	Asp	Thr	Phe	G1y	Trp	Arg	Gly	Ala	Leu	Leu	Leu	Leu
				165					170			٠		175	• •,
Gly	Ala	Ile	Thr	Leu	His	Leu	Thr	Pro	Cys	Gly	Ala	Leu	Leu	Leu	Pro
			180					185					190		
Leu	Val	Leu	Pro	Gly	Asp	Pro	Pro	Ala	Pro	Pro	Arg	Ser	Pro	Leu	Ala

	•	195				• •	200		•	•		205		•••	
Ala	Leu	Gly	Leu	Ser	Leu	Phe	Thr	Arg	Arg	Ala	Phe	Ser	Ile	Phe	Ala
	210		٠.		٠	215				•	220	ı		··. •	
Leu	Gly	Thr	Ala	Leu	Val	Gly	Gly	Gly	Tyr	Phe	Val	Pro	Tyr	Val	His
225					230					235		2			240
Leu	Ala	Pro	Arg	Phe	Arg	Pro	Gly	Pro	Gly	Gly	Ile	Arg	Ser	Ser	Ala
				245					250			•		255	٠.
Gly	Gly	Gly	Arg	Gly	Cys	Asp	Gly	Gly	Cys	Gly	Arg	Pro	Ala	Gly	Leu
	· .		260		•		٠	265					270		•
Arg	Val	Ala	Gly	Arg	Pro	Arg	Leu	Gly	Ala	Pro	Pro	Ala	Ala	Ala	Gly
	•	275					280					285			
Arg	Ile	Arg	Gly	Ser	Asp	Trp	Ala	Gly	Ala	Val	Gly	Gly	Gly	Ala	Gly
	290		•			295	.				300		•		
Ala	Arg	Gly	Gly	Arg	Arg	Arg	Glu	Leu	Gly	Gly	Ser	Pro	Ala	Gly	Arg
305		•			310		•	•		315	•	,			320
Gly	Cys	Gly	Leu	Trp	Ala	Glu	Arg	Gly	Glu	Leu	Arg	Pro	Ala	Gly	Phe
•	. : '		•	325					330			•		335	. • • •
Arg	Cys	Thr	Pro	Arg	Ala	Gly	Gly	Arg	Arg	Arg	Cys	Gly	Ala	Gly	His
.•	:		340		•	•	•	345		•			350	•	• •
Arg	Ala	Gly	Asp	Asp	Ala	Asp	Glu	Pro	Arg	Gly	Ala	Pro	Gly	Pro	Ser
		355		. <i>'</i>	•	:	360		•	•		365	•	. •	: .:
Pro	Val	Arg	Leu	Pro	Lys	Gly						:			•
, ,	370		•			375		- •		:	: .,	•		7.4	\ .
							t'								

PNEDOCID: -WO 011288042 L

<211	> 35	0					٠.								
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Pro	Glu	Trp	Gly	Gly	Phe	Glu	Glu	Asn	Ile	Gln	Gly	Gly	Gly	Ser	Ala
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Val	Ile	Asp	Met	Glu	Asn	Met	Asp	Asp	Thr	Ser	Gly	Ser	Ser	Phe	Glu
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Asp	Met	Gly	Glu	Leu	His	Gln	Arg	Leu	Arg	Glu	Glu	Glu	Val	Asp	Ala
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Asp	Ala	Ala	Asp	Ala	Ala	Ala	Ala	Glu	Glu	Glu	Asp	Gly	Glu	Phe	Leu
65					70					75					80
Gly	Met	Lys	Gly	Phe	Lys	Gly	Gln	Leu	Ser	Arg	Gln	Val	Ala	Asp	Gln
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Met	Trp	Gln	Ala	Gly	Lys	Arg	Gln	Ala	Ser	Arg	Ala	Phe	Ser	Leu	Tyr
			100					105					110		
Ala	Asn	Ile	Asp	Ile	Leu	Arg	Pro	Tyr	Phe	Asp	Val	Glu	Pro	Ala	Gln-
	.•	115		. •			120					125			
Val	Arg	Ser	Arg	Leu	Leu	Glu	Ser	Met	Ile	Pro	Ile	Lys	Met	Val	Asn
	130)			·	135					140			ů.	; ;
Phe	Pro	Gln	Lys	: Ile	Ala	Gly	Glu	Leu	Tyr	Gly	Pro	Leu	Met	Leu	Val
145	;				150)				155					160
Phe	. Thi	- Lei	ı Val	l Ala	ı Ile	e Leu	Leu	His	Gly	Met	Lys	Thr	Ser	Asp	Thr:

	165	170	175	• :
Ile Ile Arg G	Slu Gly Thr Leu	Met Gly Thr Ala	Ile Gly Thr Cys	Phe
1	80	185	190	
Gly Tyr Trp L	eu Gly Val Ser	Ser Phe Ile Tyr	Phe Leu Ala Tyr I	Leu
195		200	205	r.
Cys Asn Ala G	In Ile Thr Met	Leu Gln Met Leu A	Ala Leu Leu Gly 1	Tyr
210	215	• ;	220	
Gly Leu Phe G	ly His Cys Ile	Val Leu Phe Ile 1	Thr Tyr Asn Ile i	His
225	230	235		240
Leu His Ala Le	eu Phe Tyr Leu I	Phe Trp Leu Leu V		
	245	250	255	
Thr Leu Arg Ma		Leu Val Ser Arg 1		Γhr
	60	265	270	
				nL _
275		Thr Leu Ala Ala I 280		ne
			285	. •
		Tyr His Lys Val V		
290	295		300 100 100 100 100 100	
		Ile Pro Pro Ile G	Gln Arg Vál Pro A	lrg
305	310	315	3	320
Asp Ile Pro Al	la Met Leu Pro A	Ala Ala Arg Leu F	Pro Thr Thr Val L	.eu
	325	330	335	
Asn Ala Thr Al	la Lys Ala Val <i>A</i>	Ala Val Thr Leu G	Gln Ser His	:
34	40	345	350	
٠	6.1°	•	•	<i>¥.</i>
<210> 36	Company of the second	San Company	to the great sections	:

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<212	>, PF	RT _.		<i>:</i> ·		,									
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Met	Ser	Ser	Gln	Pro	Ala	Gly	Asn	Gln	Thr	Ser	Pro	Gly	Ala	Thr	Glu
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Asp	Tyr	Ser	Tyr	Gly	Ser	Trp	Tyr	Ile	Asp	Glu	Pro	Gln	Gly	Gly	Glu
			20					25					30		
Glu	Leu	Gln	Pro	Glu	Gly	Glu	Val	Pro	Ser	Cys	His	Thr	Ser	Ile	Pro
		35					40					45			
Pro	Gly	Leu	Tyr	His	Ala	Cys	Leu	Ala	Ser	Leu	Ser	Ile	Leu	Val	Leu
	50					55					60				
Leu	Leu	Leu	Ala	Met	Leu	Val	Arg	Arg	Arg	Gln	Leu	Trp	Pro	Asp	Cys
65					70					75					80
Val	Arg	Gly	Arg	Pro	Gly	Leu	Pro	Ser	Pro	Val	Asp	Phe	Leu	Ala	Gly
	ϵ_{i}^{\pm} ,		4	85					90					95	
Asp	Arg	Pro	Arg	Ala	Val	Pro	Ala	Ala	Väl	Phe	Met	Val	Leu	Leu	Ser
			100					105					110		
Ser	Leu	Cys	Leu	Leu	Leu	Pro	Asp	Glu	Asp	Ala	Leu	Pro	Phe	Leu	Thr
	•	115	;	•			120					125	•		
Leu	Ala	. Ser	Ala	Pro	Ser	Gln	Asp	Gly	Lys	Thr	Glu	Ala	Pro	Arg	Gly
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Ala	Tr	Lys	; Ile	. Leu	Gly	Leu	Phe	Тут	Tyr	Ala	a Ala	Leu	ı Tyr	Tyr	Pro
145	5,				150)				155	5	: '			160
Let	ı Ala	a Ala	a Cys	. Ala	1 Thr	Ala	Gly	His	Thi	r Ala	a Ala	a His	: Lei	ı Let	ı Gly

				165					170					175		•
Ser	Thr	Leu	Ser	Trp	Ala	His	Leu	Gly	Val	Gln	Val	Trp	Gln	Arg	Ala	
			180					185				:	190		.:	٠.
Glu	Cys	Pro	Gln	Val	Pro	Lys	Ile	Tyr	Lys	Tyr	Tyr	Ser	Leu	Leu	Ala	
		195					200	;			٠.	205		•	٠.	
Ser	Leu	Pro	Leu	Leu	Leu	Gly	Leu	Gly	Phe	Leu	Ser	Leu	Trp	Tyr	Pro	
	210			٠		215		٠			220			٠	, '	
Val	Gln	Leu	Val	Arg	Ser	Phe	Ser	Arg	Arg	Thr	Gly	Ala	Gly	Ser	Lys	
225					230					235	-			•	240	
Gly	Leu	Gln	Ser	Ser	Tyr	Ser	Glu	Glu	Tyr	Leu	Arg	Asn	Leu	Leu	Cys	
	. '			245					250					255		
Arg	Lys	Lys	Leu	Gly	Ser	Ser	Tyr	His	Thr	Ser	Lys	His	Gly	Phe	Leu	
			260		•			265			•	-	270			
Ser	Trp	Ala	Arg	Val	Cys	Leu	Arg	His	Cys	Ile	Tyr	Thr	Pro	Gln	Pro	,
	. •	275	•				280					285	;	•		•
Gly		His	Leu	Pro	Leu		Leu	Val	Leu	Ser		Thr	Leu	Thr	Gly	
	290					295					300	• .	•	•	:	.**
	Ala	Ile	Tyr	Gln		Ala	Leu	Leu	Leu	Leu	Val	Gly	Val	Val		
305					310					315					320	
															Leu	
															Val	
															: 1 .	
															Ser	
1.	- •	4hh					366					400	- 1			

BNSDOCID: «WO 0112660A2 1

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Ala	Leu	Val	Leu	Ser	Cys	Leu	Leu	Thr	Phe	Leu	Val	Leu	Met	Arg	Ser
	370					375					380				
Leu	Val	Thr	His	Arg	Thr	Asn	Leu	Arg	Ala	Leu	His	Arg	Gly	Ala	Ala
385	, <u>;</u>				390	•				395					400
Leu	Asp	Leu	Ser	Pro	Leu	His	Arg	Ser	Pro	His	Pro	Ser	Arg	G1n	Ala
	·			405					410					415	
Ile	Phe	Cys	Trp	Met	Ser	Phe	Ser	Ala	Tyr	Gln	Thr	Ala	Phe	Ile	Cys
	٠,		420			:		425				•	430	٠.	•
Leu	G1y	Leu	Leu	Val	Gln	Gln	Ile	Ile	Phe	Phe	Leu	Gly	Thr	Thr	Ala
		435					440					445			
Leu	Ala	Phe	Leu	Val	Leu	Met	Pro	Val	Leu	His	Gly	Arg	Asn	Leu	Leu
	450					455					460				
Leu	Phe	Arg	Ser	Leu	Glu	Ser	Ser	Trp	Pro	Phe	Trp	Leu	Thr	Leu	Ala
465					470					475					480
Leu	Ala	Val	Ile	Leu	Gln	Asn	Met	Ala	Ala	His	Trp	Val	Phe	Leu	Glu
				485					490					495	
Thr	His	Asp	Gly	His	Pro	Gln	Leu	Thr	Asn	Arg	Arg	Val	Leu	Tyr	Ala
			500)				505					510		
															Val
		.,515	5.				520	i				525	;		
Ala	Thr	Trp	Arg	g Val	Leu	Leu	Ser	Ala	Leu	Tyr	Asr	ı Ala	Ile	His	Leu
	.√ 53 0) ()			. :	538	5		÷		-540) .	. •	٠.	:
															ı Asp
54	5	ı ,			, 550)				555	5 .	· [· ·			560
Pro	o G1 :	v Tv:	r Tv	r Th	r Tvi	r Ar	g Asr	n Phe	e Let	ı Lys	s Ile	e Glu	ı Val	Ser	Gln

BNCDOCID: -WO 011366043 L

•		565					570				•	575	'
Ser His P	ro Ala	Met	Thr	Ala	Phe	Cys	Ser	Leu	Leu	Leu	Gln	Ala	Gln
. 1	580) .				585					590	:	
Ser Leu L	eu Pro	Arg	Thr	Met	Ala	Ala	Pro	Gln	Asp	Ser	Leu	Arg	Pro .
5	95				600					605		.:	
Gly Glu G	lu Asp	Glu	Gly	Met	Gln	Leu	Leu	Gln	Thr	Lys	Asp	Ser	Met
610	÷	,		615					620				. , .
Ala Lys G	ly Ala	Arg	Pro	Gly	Ala	Ser	Arg	Gly	Arg	Ala	Arg	Trp	Gly
625			630					635					640
Leu Ala T	yr Thr	Leu	Leu	His	Asn	Pro	Thr	Leu	Gln	Val	Phe	Arg	Lys
							650					655	
Thr Ala L	eu Leu	ı Gly	Ala	Asn	Gly	Ala	Gln	Pro					
	660					665							
•													
<210> 37 ⋅							,				,		4
<211> 464							•						
<212> PRT				y.	,	,							; *
<213> Hom		ens											
<400> 37								. :					
				Dha	Wa+	₩a+				۸1۵	Luc	Clar	Vo1
Met Ile V													
1													
Gln Leu V													
and the	• 20) ·	•	٠٠,	•	· 25	•	•	:	. •	30	•	sy str
Thr'Ser S													
11247 124	35	1	•		40		٠.			45		. :	9 7

Val	Leu	Ser	Tyr	Phe	Ser	Ser	His	Tyr	Pro	Pro	Ser	Ile	Ile	Leu	Ala
	50					55					60				
Lys	Glu	Ser	Tyr	Ala	Glu	Leu	Ile	Met	Lys	Leu	Leu	Lys	Val	Ser	Ala
65	٠.	٠.			70					75		<u>.</u>			80
Gly	Leu	Ser	Ile	Pro	Thr	Asp	Ser	Gln	Lys	His	Leu	Asp	Ala	Val	Pro
				85					90					95	
Lys	Cys	Gln	Ala	Phe	Thr	His	Gln	Met	Val	Gln	Phe	Leu	Ser	Thr	Leu
			100					105					110		•••
Glu	Gln	Asn	Gly	Lys	Ile	Thr	Leu	Ala	Val	Leu	Glu	Gln	Glu	Met	Ser
		115					120					125			
Lys	Leu	Leu	Asp	Asp	Ile	Ile	Val	Phe	Asn	Pro	Pro	Asp	Met	Asp	Ser
	130					135					140				
Gln	Thr	Arg	His	Met	Ala	Leu	Ser	Ser	Leu	Phe	Met	Glu	Val	Leu	Met
145			•		150					155					160
Met	Met	Asn	Asn	Ala	Thr	Ile	Pro	Thr	Ala	Glu	Phe	Leu	Arg	Gly	Ser
				165					170		,			175	
Ile	Arg	Thr	Trp	Ile	Gly	Gln	Lys	Met	His	Gly	Leu	Val	Val	Leu	Pro
			180					185					190		
Leu	. Leu	Thr	Ala	Ala	Cys	Gln	Ser	Leu	Ala	Ser	Val	Arg	His	Met	Ala
	: •	195					200					205			: *
Glu	Thr	Thr	Glu	Ala	Cys	Ile	Thr	Ala	Tyr	Phe	Lys	Glu	Ser	Pro	Leu
	210) .		•		215	;		٠,	:	220)			
Asn	Gln	Asr	Ser	Gly	Trp	Gly	Pro	Ile	Leu	Val	Ser	Leu	Gln	Val	Pro
225	5 .				230)				235	i	• :			240
C1.	. 1	. The	. Mat	. G1,	. Glu	Phe	ום [Gln	Gla	ı Cvs	: Lei	Thr	· Leu	Gly	Ser

• • • • •	245	."		250			255	• •
Tyr Leu Thr	Leu Tyr	Val Tyr	Leu L	eu Gln	Cys Le	eu Asn	Ser Glu	Gln
	260		2	65			270	
Thr Leu Arg	Asn Glu	Met Lys	: Val L	eu Leu	Ile Le	eu Ser	Lys Trp	Leu
275			280			285	,	1941 94
Glu Gln Val	Tyr Pro	Ser Ser	r Val G	lu Glu	Glu A	la Lys	Leu Phe	Leu
290		29	5		3	00		*
Trp Trp His	Gln Val	Leu Gl	n Leu S	Ser Leu	Ile G	ln Thr	Glu Gl	n Asn
305		310			315		٠	320
Asp Ser Val	l Leu Thi	r Glu Se	r Val	Ile Arg	Ile L	eu Leu	Leu Va	l Gln
	32	5	-	330			33	5 .
Ser Arg Gla	n Asn Lei	u Val Al	a Glu (Glu Arg	Leu S	er Ser	· Gly Il	e Leu
	340		;	345			350	
Gly Ala Il	e Gly Ph	e Gly Ar	g Lys	Ser Pro	Leu S	Ser Asr	ı Arg Ph	e Arg
35	5		360			365	5	4
Val Val Al	a Arg Se	r Met Al	a Ala	Phe Lev	ı Ser V	Val Gl	ı Val Pr	o Met
370		3'	75		,	380	,	
Glu Asp Gl	n Ile Ar	g Leu A	rg Pro	Gly Sea	r Glu	Leu Hi	s Leu Th	ır Pro
385		390						400
Lys Ala Gl								
. • . • • •		05						
Gln Tyr Va								
Arg His P								
	35		440	1	٠,	44	15	± 1 + 44 - 49

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Leu	(Va)	l Ası	n Cys	s Le	ı Tyr	r Pro	Glu	ı Val	His	S Tyr	Leu	ı Ası	His	Ile	Arg	
	450)				455	5				460)				
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⟨21	3> H	omo	sapi	ens												
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Met	Ser	Arg	Leu	Gly	Ala	Leu	Gly	Gly	Ala	Arg	Ala	Gly	Leu	Gly	Leu	
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Leu	Leu	Gly	Thr	Ala	Ala	Gly	Leu	Gly	Phe	Leu	Cys	Leu	Leu	Tyr	Ser	
	•		20					25				-	30			
Gln	Arg	Trp	Lys	Arg	Thr	Gln	Árg	His	Gly	Arg	Ser	Gln	Ser	Leu	Pro	
		35					40					45				
Asn	Ser	Leu	Asp	Tyr	Thr	Gln	Thr	Ser	Asp	Pro	Gly	Arg	His	Val	Met	
	50	٠.,	•			55					60				٠.	
Leu	Leu	Arg	Ala	Val	Pro	Gly	Gly	Ala	Gly	Asp	Ala	Ser	Val	Leu	Pro	
65 .					70					75					80	
Ser	Leu											Arg	Leu	Asp.	Phe	
	13													95		
													Glu			
													110			
Ser	Ser	Leu	Arg	Gly	Leu	Ala	Gly	Glu	Ile	Val	G1y	Glu	Val	Arg	Cys	
His	Met	Glu	Glu	Asn	Gln	Aro	Va1	412	Ara	A	4	A ~~~	Dha	D	Dha	

	130	•	.		, •	135			•••		140	•			
Val	Arg	Glu	Arg	Ser	Asp	Ser	Thr	Gly	Ser ·	Ser	Ser	Val	Tyr	Phe	Thr
145		•			150					155					160
Ala	Ser	Ser	Gly	Ala	Thr	Phe	Thr	Asp	Ala	Glu	Ser	Glu	Gly	Gly	Tyr
				165					170					175	
Thr	Thr	Ala	Asn	Ala	'G1u	Ser	Asp	Asn	Glu	Arg	Asp	Ser	Asp	Lys	Glu
		٠	180					185					190	٠.	
Ser	Glu	Asp	Gly	Glu	Asp	Glu	Val	Ser	Cys	Glu	Thr	Val	Lys	Met	Gly
	:	195			٠.		200			•		205			·. '
Are	g Lys	Asp	Ser	Leu	Asp	Leu	Glu	Glu	Glu	Ala	Ala	Ser	Gly	Ala	Ser
	210)				215					220				•
Sei	. Ala	. Leu	Glu	Ala	Gly	Gly	Ser	Ser	Gly	Leu	Glu	Asp	Val	Leu	Pro
229	5				230	•			٠	235					240
Lei	ı Lev	ı Glr	Gln	Ala	Asp	Glu	Leu	His	Arg	Gly	Asp	Glu	Gln	Gly	Lys
			,	245	;				250			ı	•	255	, ·
Ar	g Glu	ı Gly	r Phe	e Gln	Leu	ı Leu	Leu	Asn	Asn	Lys	Leu	Val	Tyr	Gly	Ser
			260)		٠.		265	;		-		270	,	
Ar	g Gl	n Ası	Phe	e Leu	ı Trp	Are	Leu	Ala	Arg	, Ala	Tyr	Ser	Asp	Met	Cys
		279	5				280)		٠.		285	5	-	
Gl	u Le	u Th	r Glo	u Glu	ı Va	l Sei	Glu	Lys	Lys	s Ser	Tyr	Ala	Leu	Ası	Gly
	29	0.	٠.			298	5		٠.		300			• •	• •
Ly	s Gl	u Gl	u Al	a Gl	u Al	a Ala	a Leu	ı Glu	ı Lys	s Gly	y Asp	Glu	ı Ser	· Ala	a Asp
30)5	•		٠,	31	0				31	5				320
Cy	rs Hi	s Le	u Tr	р Ту	r Al	a Va	l Lei	ı Cy:	s Gl	y Gl	n Lei	ı Ala	a Glu	ı Hi	s Glu
	٠,٠			32	5		ı		33	0				· 33	5 :

Ser Ile Gln Arg Arg Ile Gln Ser Gly Phe Ser Phe Lys Glu His Val
340 345 350
Asp Lys Ala Ile Ala Leu Gln Pro Glu Asn Pro Met Ala His Phe Leu
355 360 365
Leu Gly Arg Trp Cys Tyr Gln Val Ser His Leu Ser Trp Leu Glu Lys
370 375 380
Lys Thr Ala Thr Ala Leu Leu Glu Ser Pro Leu Ser Ala Thr Val Glu
385 390 395 400
Asp Ala Leu Gln Ser Phe Leu Lys Ala Glu Glu Leu Gln Pro Gly Phe
405 410 415
Ser Lys Ala Gly Arg Val Tyr Ile Ser Lys Cys Tyr Arg Glu Leu Gly
420 425 430
Lys Asn Ser Glu Ala Arg Trp Trp Met Lys Leu Ala Leu Glu Leu Pro
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⟨211⟩ 243
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1			÷	5					10	•		k.		·15	
Ser	Val	Thr	Pro	Tyr	Thr	Pro	Ser	Thr	Ala	Asp	Ile	Gln	Val	Ser	Asp
	•		20					25				,	30	,	
Asp	Asp	Lys	Ala	Gly	Ala	Thr	Leu	Leu	Phe	Ser	Gly	Ile	Phe	Leu	Gly
	• ;	35					40					45		•	200
Leu	Val	Gly	Ile	Thr	Phe	Thr	Val	Met	Gly	Trp	Ile	Lys	Tyr	Gln	Gly
	50					55				*	60				•
Val			Phe	Glu	Trp	Thr	Gln	Leu	Leu	Gly	Pro	Val	Leu	Leu	Ser
65					70					75					80
		. Val	Thr	· Phe	Ile	Leu	Ile	Ala	Val	Cys	Lys	Phe	Lys	Met	Leu
	,			. 85					90					95	
Ser	- Cvs	s Glr	ı Leu	ı Cys	Lys	: Glu	. Ser	Glu	Glu	Arg	Val	Pro	Asp	Ser	Glu
			100					105					110		
Gli	ı Thi	r Pro			, Pro	Ser	- Phe	e Val	Phe	. Thi	- Gly	, Ile	e Ası	n Glr	n Pro
01.		115					120					129			r ,
11.	e Th			s Gl	v Ala	a Thi	r Val	l Val	Glr	n Tyi	r Il	e Pro	o Pro	o Pro	o Tyr
11.	13		-		•	13					14			, ,	
C1			o G1	u Pr	o Me			e Ası	n Thi	r Se	r Ty	r Le	u Gl	n Se	r Val
14				• • •	15		•			15					160
		r Pr	n Cv	s Gl			e Th	r Se	r Gl	y Gl	y Al	a Al	a Al	a Al	a Met
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Ç.	- C.	. D.	Dr			r Tu	r ፕե	r 11			o G1	n As	p As	n Se	er Ala
26	:r 36	:I TI			. 11 г. ј	y	_ 11	18		- ••					· . !!!
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Pł	ne Va	at As	ai As	sp G	Lu G	y U	SLE	su st	1 1 1	10 11		. ت بر	-,		

Ar	g Pr	o As	n Pr	o A	sp	Val	Asp	Glr	Le	u Gl	ı Glı	ı Thi	r Gl	n Le	u Gl	u Glu
	21	0					215			•		220)		•	
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<213> Homo sapiens

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BUSTOCIO--WO 011288082 I .

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cagctggaag	aggaggcctg	tgcctgcttc	tetectecce	cttatgaaga	aatatactct ·	720
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gatgacatga	a aatgggccc	a gaagatcaa	a	· * * * * * * * * * * * * * * * * * * *	r yydus feithi	810

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<211>	155	1			•										•	•
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										Me	t Ası	Se:	r Ala	a Le	u Ser	
	-									3	1			!	5	
gat c	cg ca	at	aac	ggc	agt	gcc	gag	gca	ggc	ggc	ccc	acc	aac	agc	act	163
Asp P	ro Hi	s	Asn	Gly	Ser	Ala	Glu	Ala	Gly	Gly	Pro	Thr	Asn	Ser	Thr	
••,•		-	10				•	15					20			
acg c	gg co	g	cct	tcc	acg	ccc	gag	ggc	atc	gcg	ctg	gcc	tac	ggc	agc -	211
Thr A	rg Pr	ю	Pro	Ser	Thr	Pro	Glu	Gly	Ile	Ala	Leu	Ala	Tyr	Gly	Ser	
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ctc c	tg ct	c·	atg	gcg	ctg	ctg	ссс	atc	ttc	ttc	ggc	gcc	ctg	cgc	tcc	259
Leu L	eu Le	eu	Met	Ala	Leu	Leu	Pro	Ile	Phe	Phe	Gly	Ala	Leu	Arg	Ser	
(7,)	40 -	•	· •		. •	45					50	. ,			٠.	
gta c	gc . tg	ζC	gcc	cgc	ggc	aag	aat	gct	tca	gac	atg	cct	gaa	aca	atc	307
Val A	rg Cy	'S	Ala	Arg	Gly	Lys	Asn	Ala	Ser	Asp	Met	Pro	Glu	Thr	Ile	
55 ·		. ·.	·		- 60				<u>.</u>	65					70	

acc	agc	cgg	gat	gcc	gcc	cgc	ttc	ccc	atc	atc	gcc	agc	tgc	aca	ctc	355
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Leu	Gly	Leu	Tyr	Leu	Phe	Phe	Lys	Ile	Phe	Ser	Gln	Glu	Tyr	Ile	Asn	
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cac	acc	atc	agc	ccc	ttc	atg	aat	aag	ttt	ttt	cca	gcc	ago	ttt	cca	499:)
His	Thr	Ile	Ser	Pro	Phe	Met	Asn	Lys	Phe	Phe	Pro	Ala	Ser	Phe	Pro	4
	120					125					130	•	,			•
aat	cga	cag	tac	cag	ctg	ctc	ttc	aca	cag	ggt	tct	ggg	g gaa	a aad	aag	547
Asn	Arg	Gln	Tyr	· Gln	Leu	Leu	Phe	Thr	Gln	Gly	Ser	Gly	Glu	ı Ası	n Lys	• :-
135	;· ·				140)				145			•		150	F-,
gaa	gag	ato	ato	aat	tat	gaa	ttt	gac	acc	aag	gac	cte	g gt	g tg	c ctg	595
Glu	ı Glu	ı Ile	e Ile	a Asn	Tyr	Glu	. Phe	Asp	Thr	Lys	Asp	Let	ı Va	1 · Cy	s Leu	ı
				155	5 ,				160)			٠.	16	5	
gg	c ct	giago	c ago	ato	gtt	t ggo	gto	tgg	g tac	ctg	g ctg	g ag	g aa	g ca	c tgg	g 643
G1:	y Lei	u Se	r Sei	r Ile	e Val	l G1;	y Val	Tr	р Туз	r Leu	ı Lei	u Ar	g Ly	s Hi	s Trp	•
		· * •	17	0 '				17	5			-	18	0	•. •.	. "
at	t gc	c aa	c aa	c ct	t tt	t gg	c ct	g gc	c tte	c tc	c ct	t aa	t gg	a gt	a ga	g 691
															al Gl	
															37	
·ct	c ct	g ca	ıc ct	.с аа	c aa	t gt	c ag	c ac	t gg	c tg	c at	c ct	g ct	g g	gc gg	a [.] 739

Leu	Leu	His	Leu	Asn	Asn	Val	Ser	Thr	Gly	Cys	Ile	Leu	Leu	Gly	Gly	
	200		e			205					210					-
ctc	ttc	atc	tac	gat	gtc	ttc	tgg	gta	ttt	ggc	acc	aat	gtg	atg	gtg	783
Leu	Phe	Ile	Tyr	Asp	Val	Phe	Trp	Val	Phe	Gly	Thr	Asn	Val	Met	Val	
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Phe	Asp	Ile	Ser	Leu	Lys	Lys	Asn	Thr	His	Thr	Tyr	Phe	Tyr	Thr	Ser	
	280					285					290				:	
ttt	gca	gcc	tac	atc	ttc	ggc	ctg	ggc	ctt	acc	atc	ttc	atc	atg	cac	1027
Phe	Ala	Ala	Tyr	Ile	Phe	Gly	Leu	Gly	Leu	Thr	Ile	Phe	Ile	Met	His	
295					300					305		٠			,310	
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Ile	Phe	Lys	His	Ala	Gln	Pro	Ala	Leu	Leu	Tyr	Leu	Val	Pro	Ala	Cys	
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Ile	Gly.	Phe	Pro	Val	Leu	Val.	Ala	Leu.	Ala	Lys	Glv	Glu	Val	Thr	Glu	

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Glu Ser Lys Glu Gly Thr Glu Ala Ser Ala Ser Lys Gly Leu Glu Lys	
360 365 370	
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Lys Glu Lys	
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Pro Val Ile Ile Phe Thr Thr Phe Trp Gly Leu Val Gly Ile Ala Gly	
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Pro Trp Phe Val Pro Lys Gly Pro Asn Arg Gly Val Ile Ile Thr Met	
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Leu Val Ala Thr Ala Val Cys Cys Tyr Leu Phe Trp Leu Ile Ala Ile	
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Leu Ala Gln Leu Asn Pro Leu Phe Gly Pro Gln Leu Lys Asn Glu Thr	
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Ile Trp Tyr Val Arg Phe Leu Trp Glu	
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104/307

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ggaį	ggaaa	ac a	tg g	gg ga	at a	ct g	gc c1	tg ag	ga a	ag c	gg ag	ga g	ag g	at g	ag		228
		. Me	et G	Ly A	sp Tl	hr G	ly Le	eu Ai	rg L	ys Ao	rg Ai	rg G	lu A	sp G	lu		
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aag	tcg	atc	cag	agc	caa	gag	cct	aag	acc	acc	agt	ctc	caa	aag	gag		276
Lys	Ser	Ile	Gln	Ser	Gln	Glu	Pro	Lys	Thr	Thr	Ser	Leu	Gln	Lys	Glu		
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ctg	ggc	ctc	atc	agt	ggc	atc	tcc	atc	atc	gtg	ggc	acc	atc	att	ggc		324
Leu	Gly	Leu	Ile	Ser	Gly	Ile	Ser	Ile	Ile	Val	Gly	Thr	Ile	Ile	Gly		
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tct	ggg	atc	ttc	gtt	tcc	ccc	aag	tct	gtg	ctc	agc	aac	acg	gaa	gct		372
Ser	Gly	Ile	Phe	Val	Ser	Pro	Lys	Ser	Val	Leu	Ser	Asn	Thr	Glu	Ala		
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gtg	ggg	ccc	tgc	ctc	atc	ata	tgg	gcg	gct	tgc	ggg	gtc	ctc	gcg	acg		420
Val	Gly	Pro	Cys	Leu	Ile	Ile	Trp	Ala	Ala	Cys	Gly	Val	Leu	Ala	Thr		
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ctg	ggt	gcc	ctg	tgc	ttt	gcg	gag	ctt	ggc	aca	atg	atc	acc	aag	tca		468
Leu	Gly	Ala	Leu	Cys	Phe	Ala	Glu	Leu	Gly	Thr	Met	Ile	Thr	Lys	Ser		
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Gly	Gly	Glu	Tyr	Pro	Tyr	Leu	Met	Glu	Ala	Tyr	Gly	Pro	Ile	Pro	Ala		
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gcc	atc	atc	tgc	ctc	agc	ttc	tcc	gag	tat	gtg	tgt	gcg	ccc	ttc	tat.	•	512
Ala	Ile	Ile	Cys	Leu	Ser	Phe	Ser	Glu	Tyr	Val	Cys	Ala	Pro	Phe	Tyr		
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Val	Gly	Cys	Lys	Pro	Pro	G1n	Ile	Val	Val.	Lys	Cys	Leu	Ala	Ala	Ala		
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gcc	atc	ttg	ttc	atc	tcg	aca	gtg	aac	tca	ctg	agc	gtg	cgg	ctg	gga	•	708
Ala	Ile	Leu	Phe	Ile	Ser	Thr	Val	Asn	Ser	Leu	Ser	Val	Arg	Leu	Gly		1 ,
	-	160					165					170		•			
agc	tac	gtc	cag	aac	atc	ttc	acc	gcg	gcc	aag	ctg	gtg	atc	gtg	gcc.		756
Ser	Tyr	Val	Gln	Asn	Ile	Phe	Thr	Ala	Ala	Lys	Leu	Val	Ile	· Val	Ala.		
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Ile	Ile	Ile	lle	Ser	Gly	Leu	Val	Leu	Leu	Ala	Gln				Lys		
					195										205.		
								•							atc		852
															a Ile	•	
) ;'	•	000
															t caa		900
															n Gln.		
													•		[] (1) Y	•	0.40
															g cct		948
Le	u As	п Ту	r Il	e Th	r Gl	u Gl	u Lei	ı Arı	g Ası	n Pro	о Ту	r Ar	g As	n Le	u.Pro	•	

BRIGHTONIN- JWO - MITSRENAS I -

معاملات الكارات والميارات

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	255					260					265			-	-	
atg	aac	gtg	tcc	tac	ttc	acc	gtg	atg	act	gcc	acc	gaa	ctc	ctg	cag	1044
Met	Asn	Val	Ser	Tyr	Phe	Thr	Val	Met	Thr	Ala	Thr	Glu	Leu	Leu	Gln	
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Ser	Gln	Ala	Val	Ala	Val	Thr	Phe	Gly	Asp	Arg	Val	Leu	Tyr	Pro	Ala	
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tct	tigg	atc	gtt	cca	ctt	ttt	gtg	gca	ttt	tca	acc	atc	ggt	gct	gct	1140
Ser	Trp	Ile	Val	Pro	Leu	Phe	Val	Ala	Phe	Ser	Thr	Ile	Gly	Ala	Ala	
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Asn	Gly	Thr	Cys	Phe	Thr	Ala	Gly	Arg	Leu	Ile	Tyr	Val	Ala	Gly	Arg	
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Glu	Gly	His	Met	Leu	Lys	Val	Leu	Ser	Tyr	Ile	Ser	Val	Arg	Arg	Leu	
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Glu	Val	Val	Pro	Pro	Glu	Glu	. Asp	Pro	°G1u	١.					•. •	
)													
ago	caag	gtca	gctg	gaatt	ta t	ttt	ttaa	ng ca	atat	ttgt	ggt:	tati	tct	tcc1	ttttt	1730
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				. ,							Ме	t Al	a Th	r Th	r Ala	•	
	: -	.:			٠.					. •		1 .		. ,	<i>₹ .a</i> 5	٠ .	
ac	· a · c c	ים סו	0 00	7C. 99	2C 22	c ce	a aa	at gg	a go	t gg	c cc	g ga	a te	g g	a ggg	;	163

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Al	a Va	l Le	u Va	1 Se	r Ar	g Tha	· Va	1 G1	y Pro	Thi	c Gl	n Arı	g Le	u Le	u Leu	٠
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Leu	Pro	Phe	Leu	Thr	Leu	Ala	Ser	Ala	Pro	Ser	Gln	Asp	Gly	Lys	Thr	
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gag	gct	cca	aga	ggg	gcc	tgg	aag	ata	ctg	gga	ctg	ttc	tat	tat	gct	544
Glu	Ala	Pro	Arg	Gly	Ala	Trp	Lys	Ile	Leu	Gly	Leu	Phe	Tyr	Tyr	Ala	
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Ala	Leu	Tyr	Tyr	Pro	Leu	Ala	Ala	Cys	Ala	Thr	Ala	Gly	His	Thr	Ala	
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Ala	His	Leu	Leu	Gly	Ser	Thr	Leu	Ser	Trp	Ala.	His	Leu	Gly	Val	Gln _.	
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Val	Trp	Gln	Arg	Ala	G1u	Cys	Pro	Gln	Val	Pro	Lys	Ile	Tyr	Lys	Tyr	
-		190					195		٠			200		• :		
tac,	tcc	ctg	ctg	gcc	tcc	ctg	cct	ctc	ctg	ctg	ggc	ctc	gga	ttc	ctg	736
Tyr	Ser	Leu	Leu	Ala	Ser	Leu	Pro	Leu	Leu	Leu	Gly	Leu	Gly	Phe	Leu	
٠.	205,	• .			ı	210			٠		215					
agc	ctt	tgg	.tac	cct	gtg	cag	ctg	gtg	aga	agc	ttç	agc	cgt	agg	aca	784
Ser	Leu	Trp	Tyr	Pro	Val	Gln	Leu	Val	Arg	Ser	Phe	Ser	Arg	Arg	Thr	

220	• • •	225			230	in the second	235 .
gga gca	ggc tcc	aag ggg	ctg cag	agc agc	tac tct	gag gaa tat	ctg 832 .
Gly Ala	Gly Ser	Lys Gly	Leu Gln	Ser Ser	Tyr Ser	Glu Glu Týr	Leu
÷	1	240		245	· ·	250	
agg aac	ctc ctt	tgc agg	aag aag	ctg gga	agc agc	tac cac acc	tcc 880
Arg Asn	Leu Leu	Cys Arg	Lys Lys	Leu Gly	Ser Ser	Tyr His Thr	Ser
•	255			260		265	
aag cat	ggc ttc	ctg tcc	tgg gcc	cgc gto	tgc ttg	aga cac tgc	atc 928
Lys His	Gly Phe	Leu Ser	Trp Ala	Arg Val	l Cys Leu	Arg His Cys	Ile
	270	•	275	;		280	20 · 10 · 10 · 10 · 10 · 10 · 10 · 10 ·
tac act	cca cag	cca gga	ttc cat	ctc cc	g ctg aag	ctg gtg ctt	tca 976
Tyr Thr	Pro Gln	Pro Gly	Phe His	Leu Pr	o Leu Lys	Leu Val Leu	Ser
285			290		295	•	•
gct aca	ctg aca	ggg acg	gcc att	tac ca	g gtg gcc	ctg ctg ctg	ctg 1024
Ala Thr	Leu Thr	Gly Thr	· Ala Ile	Tyr Gl	n Val Ala	Leu Leu Lei	Leu
300		305	; ·		310	*	315
gtg ggc	gtg gta	ccc act	atc cas	g aag gt	g agg gca	ggg gtc acc	e acg 1072
Val Gly	Val Val	Pro Thi	· Ile Gl	n Lys Va	l Arg Ala	Gly Val Th	Thr
٠, ٠		320		32	5 ` ′ ′ ′	330) ·
gat gtc	tcc tac	ctg ct	g gcc gg	c ttt gg	a atc gt	g ctc tcc ga	g gac 1120
Asp Val	Ser Tyr	Leu Le	u Ala Gl	y Phe Gl	y Ile Va	l Leu Ser Gl	ı Asp
	338	5		340		345	and the co
aag cag	gag gtg	g gtg ga	g ctg gt	g aag ca	ac cat ct	g tgg gct ct	g gaa 1168
Lys Glr	i Glu Va	l Val Gl	u Leu Va	l Lys H	s His Le	u Trp Ala Le	u Gl ù
2020 3	350	· • • • • • • • • • • • • • • • • • • •	35	5	, i , .	360	C. C

gtg	tgc	tac	atc	tca	gcc	ttg	gtc	ttø	tcc	tec	tta	ctc	800	ttc	ctø	1216
										_					_	
vai					Ala		vai	Leu	Ser	Cys		Leu	inr	rne	Leu .	
٠,	365	•	•	. ·		370					375			•		
gtc	ctg	atg	cgc	tca	ctg	gtg	aca	cac	agg	acc	aac	ctt	cga	gct	ctg	1264
Val	Leu	Met	Arg	Ser	Leu	Val	Thr	His	Arg	Thr	Asn	Leu	Arg	Ala	Leu	
380	-				385					390					395	
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His	Arg	Gly	Ala	Ala	Leu	Asp	Leu	Ser	Pro	Leu	His	Arg	Ser	Pro	His	
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ccc	tcc	cgc	caa	gcc	ata	ttc	tgt	tgg	atg	agc	ttc	agt	gcc	tac	cag	1360
					Ile										_	
	001				110		0,3	•	iiic c	JCI	1110	Jei		.,.	JIII	
	•		415					420					425			
aca	gcc .	ttt	atc	tgc	ctt	ggg	ctc	ctg	gtg	cag	cag	atc	atc	ttc	ttc	1408
Thr	Ala	Phe	Ile	Cys	Leu	Gly	Leu	Leu	Val	Gln	Gln	Ile	Ile	Phe	Phe	
		430					435					440	-			
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Leu	Gly	Thr	Thr	Ala	Leu	Ala	Phe	Leu	Val	Leu	Met	Pro	Val	Leu	His	
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Gly	Arg	Asn	Leu	Leu	Leu	Phe	Arg	Ser	Leu	Glu	Ser	Ser	Trp	Pro	Phe	
							J								475	
																1550
					ctg				_			_				1552
					Leu					Gln	Asn	Met	Ala	Ala	His	
<i>i:</i>	J*€.*			480	•		•		485		*:		•	490		
tgg	gtc	ttc	ctg	gag	act	cat	gat	gga	cac	cca	cag	ctg	acc	aac	cgg	1600

BMCDCID - MIC 011366043 1

Trp '	Val	Phe	Leu	Glu	Thr	His	Asp	Gly	His	Pro	Gln	Leu	Thr	Asn	Arg	
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cga	gtg	ctc	tat	gca	gcc	acc	ttt	ctt	ctc	ttc	ccc	ctc	aat	gtg	ctg	1648
Arg	Val	Leu-	Tyr-	Ala	Ala	Thr	Phe	Leu	Leu	Phe	Pro	Leu	Asn	Val	Leu	
.,		510	٠.				515			•		520				
gtg	ggt	gcc	atg	gtg	gcc	acc	tgg	cga	gtg	ctc	ctc	tct	gcc	ctc	tac	1696
		•				Thr										
	525					530	•	_			535					
		a ta	000	c++	aac	cag	ato	gac	ctc	agc		ctg	cca	ccg	aga	1744
Asn	Ala	He	His	Leu	Gly	Gln	Met	ASP	Leu		Leu	Leu	110	110		7;
540					545					550				•	555	
gcc	gcc	act	ctc	gac	ccc	ggc	tac	tac	acg	tac	cga	aac	ttc	ttg	aag	1792
Ala	Ala	Thr	Leu	Asp	Pro	Gly	Tyr	Tyr	Thr	Tyr	Arg	Asn	Phe	Leu	Lys	
				560)				565					570	·.	
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Ile	Glu	Val	Ser	Glr	Ser	His	Pro	Ala	Met	Thr	Ala	Phe	Cys	Ser	Leu	•
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ctc	cte	caa	gcs	cas	z ago	ctc	cta	ccc	age	g acc	ate	g gca	a gcc	ccc	cag	1888
															Gln	
		590					595						0 .			
											- 4					1936
															a cag	1950
Asp	Set	r Lei	ı Arı	g Pr	o G1	y Glu	ı Glı	ı Ası	o Glu	ı Gly	y Me	t Gl	n Lei	ı Lei	u Gln	
	60	5 ·				610) .	•			61	5				
aca	aa	g ga	c to	c at	g gc	c aag	g gg	a gc	t ag	g cc	c gg	g gc	c ag	c cg	c ggc	1984
·Thr	Ly	s As	p Se	r Me	t Al	a Lys	s Gl	y Al	a Ar	g Pr	o Gl	y Al	a Se	r Ar	g Gly	

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121/307

620	625	630	635
agg gct cgc tgg ggt	ctg gcc tac acg ctg	ctg cac aac cca	acc ctg 2032
Arg Ala Arg Trp Gly	Leu Ala Tyr Thr Leu	Leu His Asn Pro	Thr Leu
640	645		650
cag gtc ttc cgc aag	acg gcc ctg ttg ggt	gcc aat ggt gcc	cag ccc 2080
Gln Val Phe Arg Lys	Thr Ala Leu Leu Gly	Ala Asn Gly Ala	Gln Pro
655	660	665	
tgagggcagg gaaggtca	aac ccacctgccc atctg	tgctg aggcatgttc	2130
ctgcctacca tcctcctc	ce teeceggete teetee	cagc atcacaccag c	catgcagcc 2190
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cctgcagggc agcccaagt	to atgactcaga ccaggto	cca cactgagetg c	ccacactcg 2610
agagccagat attttgta	ig tttttatgcc tttggcf	tatt atgaaagagg t	tagtgtgtt 2670
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	·		4
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Met Ile Val Cys Leu Leu Phe Met Met Ile	
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tta ttg gca aag gaa gtt caa ctg gta gac caa aca gat tca cct tta	160
Leu Leu Ala Lys Glu Val Gln Leu Val Asp Gln Thr Asp Ser Pro Leu	
20 25	
ctt agt ctc ctt gga cag aca agc tca ctt tca tgg cat ctt gtg gat	208
Leu Ser Leu Leu Gly Gln Thr Ser Ser Leu Ser Trp His Leu Val Asp	
30 35 40	
att gtg tcg tac cag agt gtg cta agt tat ttc agc agc cat tac ccg	256
Ile Val Ser Tyr Gln Ser Val Leu Ser Tyr Phe Ser Ser His Tyr Pro	
ccg tcc atc atc ctg gca aaa gaa tct tat gct gaa tta atc atg aag	304
Pro Ser Ile Ile Leu Ala Lys Glu Ser Tyr Ala Glu Leu Ile Met Lys	
60 65 70	
ctc cta aaa gtg tct gcg ggc ctt tct att cct act gac agc cag aag	352
Leu Leu Lys Val Ser Ala Gly Leu Ser Ile Pro Thr Asp Ser Gln Lys	
75 80 85 90	
cat ctt gat gca gtt cca aaa tgc caa gct ttt act cat cag atgigtt	400
His Leu Asp Ala Val Pro Lys Cys Gln Ala Phe Thr His Gln Met: Val	
95 100 105	

caa ttc ctc agc acc ctg gaa caa aat gga aaa atc acc tta gca gtc

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Gln	Phe	Leu	Ser	Thr	Leu	Glu	Gln	Asn	Gly	Lys	Ile	Thr	Leu	Ala	Val :		
	-		110					115					120		٠.		
cta	gaa	cag	gaa	atg	tct	aag	ctc	tta	gac	gat	atc	att	gtc	ttt	aac		496
Leu	Glu	Gln	Glu	Met	Ser	Lys	Leu	Leu	Asp	Asp	Ile	Ile	Val	Phe	Asn		
		125					130					135					
ccg	ccc	gac	atg	gac	agc	cag	acc	cgc	cac	atg	gcc	ctc	agc	agc	ctc		544
Pro	Pro	Asp	Met	Asp	Ser	Gln	Thr	Arg	His	Met	Ala	Leu	Ser	Ser	Leu		
	140					145					150						
ttt	atg	gaa	gtc	ctg	atg	atg	atg	aac	aac	gcg	act	att	cca	aca	gca		592
Phe	Met	Glu	Val	Leu	Met	Met	Met	Asn	Asn	Ala	Thr	Ile	Pro	Thr	Ala		
155					160		•			165					170		
gag	ttc	ctt	cgg	ggc	agt	atc	cgg	acc	tgg	att	ggc	caa	aaa	atg	cat		640
Glu	Phe	Leu	Arg	Gly	Ser	Ile	Arg	Thr	Trp	Ile	Gly	Gln	Lys	Met	His		
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ggg	ctg	gtg	gtg	ctg	ccc	ctt	tta	aca	gca	gcc	tgc	cag	agc	ctg	gcg		688
Gly	Leu	Val	Val	Leu	Pro	Leu	Leu	Thr	Ala	Ala	Cys	Gln	Ser	Leu	Ala	÷	
•			190		•			195			•		200		-		
tcc	gtc	cgc	cac	atg	gct	gag	act	aca	gaa	gcc	tgc	atc	act	gcc	tac		736
Ser	Val	Arg	His	Met	Ala	Glu	Thr	Thr	Glu	Ala	Cys	Ile	Thir	Ala	Tyr		
		.205	• •	•			210	•				215					
ttc-	aaa	gaa	agc	cct	ctc	aat	cag	aat	tca	gga	tgg	gga	ccc	att	ctg		784
Phe	Lys	Glu	Ser	Pro	Leu	Asn	Gln	Asn	Ser	Gly	Trp	Gly	Pro	Ile	Leu		
•	220					225	7		ē		230						
gta	tcc	ctt	cag	gtt	ccc	gag	ctc	acc	atg	gaa	gag	ttc	ctg	cag	gag		832
Va1	Can	1	Cln	Va 1	D	C10	Lou	TL.	M-+	C1	C1	DL.	1	C1_	C1		

235	• •	•	•	•	240		·			245				•	250	
tgc	ctc	acc	ttg	ggc	agt	tac	ttg	act	ctt	tac	gtc	tac	ttg	ctt	cag	880
Cys	Leu	Thr	Leu	Gly	Ser	Tyr	Leu	Thr	Leu	Tyr	Val	Tyr	Leu	Leu	Gln	
:				255					260					265	•	
tgt	tta	aac	agc	gaa	cag	act	tta	agg	aat	gaa	atg	aaa	gtg	ctg	ctc	928
Cys	Leu	Asn	Ser	Glu	Gln	Thr	Leu	Arg	Asn	Glu	Met	Lys	Val	Leu	Leu	
			270					275				,	280			
atc	tta	agc	aag	tgg	ctg	gaa	cag	gtg	tac	cca	agc	tcc	gtg	gag	gaa	976
Ile	Leu	Ser	Lys	Trp	Leu	Glu	Gln	Val	Tyr	Pro	Ser	Ser	Val	Glu	Glu	•
	-	285	ı				290					295				
gag	gca	aag	ctg	ttt	ttg	tgg	tgg	cac	caa	gtc	ctt	cag	cto	tco	ctc	1024
Glu	Ala	Lys	Leu	Phe	Leu	Trp	Trp	His	Gln	Val	Leu	G1n	Leu	s Ser	Leu	. •
	· 300)	•			305	ı				310					
att	cag	aca	gag	cag	g aat	gac	tcc	gto	ctg	aca	gaa	tct	gto	ati	t cga	1072
Ile	Glr	1 Thr	Glu	ı 'G1r	n Asn	Asp	Ser	Val	Leu	Thr	Glu	ı Ser	· Va	l· Ile	e Arg	
315	5			.1 .	320)				325	5			•	330	•
att	cte	g cto	c tts	g gt	t cag	gago	age	g cag	g aac	cto	gt	g gc	t ga	g ga	g aga	1120
Ile	e Lei	u Lei	u Lei	ı Va	l Glı	n Sei	Arg	g Glı	n Asr	Leu	ı Va	l Ala	a Gl	u Gl	u Arg	5 `
				. 33	5	•			340) '				34	5	- t
cte	c ag	c tc	t gg	g at	c ct	g gg:	g gc	a at	t gg(g tt	t gg	c cg	g aa	g tc	g cct	1168
Le	u Se	r Se	r Gl	y Il	e Le	u Gl	y Al	a Il	e Gl	y Ph	e Gl	y Ar	g Ly	s Se	r Pro	o;
:		. 2	35	0.	. , .			35	5	ī. ·	•	•	36	iO '		•
tt	g tc	t aa	c ag	g tt	c cg	a gt	g gt	t gc	c cg	a ag	c at	g go	t go	c tt	c ct	t 1216
Le	u Se	r As	n Ar	g Ph	ne Ar	g Va	l Va	1 A1	a Ar	g Se	r Me	t Al	a Al	la' Pł	ne Le	u
•	:	36	S Ś	, , ,	• . •		37	0	••.	. '	r,	37	75	• • .	sil. 3	1

tca	gtt	cag	gtt	cct	atg	gaa	gat	cag	atc	cgt	ttg	agg	cct	ggc	tct	1264
Ser	Val	Gln	Val	Pro	Met	Glu	Asp	Gln	Ile	Arg	Leu	Arg	Pro	Gly	Ser	
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gaa	tta	cat	ctg	acc	ссс	aaa	gct	cag	cag	gct	ctg	aat	gct	ctt	gaa	1312
Glu	Leu	His	Leu	Thr	Pro	Lys	Ala	G1n	Gln	Ala	Leu	Asn	Ala	Leu	Glu	
395					400					405					410	
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Ser	Met	Ala	Ser	Ser	Lys	Gln	Tyr	Val	Glu	Tyr	Gln	Asp	Gln	Ile	Leu	
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Lys	Ser	Phe	Leu	Ala	Leu	Leu	Val	Asn	Cys	Leu	Tyr	Pro	Glu	Val	His	
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Tyr	Leu	Asp	His	Ile	Arg											
	460															
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PNSDOCID: WO 011266042 L

MARKET KROSTAN

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Gli	i Val	Tle	Leu	Arg	g Asp)	•			•		٠.	•		. ,,,	
469	. .				470				•	•	•	,	٠.	4 / 4	.:	
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Pr	o Pr	o Pr	о Ту	r Gl	y Se	r Pr	o Gl	u Pr	o Me	t Gl	y ¹Il	e As	n Th	ır Se	r Tyr	
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His	Val	Ser	Pro	His	Glu	Thr	Tyr	Phe	Cys	Ile	Thr	Thr	Gly	Trp	Leu .	
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Asn	Tyr	Pro	Leu	Glu	Lys	Ile	Gly	Phe	Trp	Arg	Arg	Leu	Glu	Asp	Leú	
	235					240					245	.:		·: '		
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Ile	Gln	Gly	Leu	Thr	Gly	Glu	Lys	Pro	Arg	Ala	Asp	Asp	Met	Lys	Trp:	
250	, ·			·	255	•				260		• •			265	
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Ala	Gln	Lys	Ile	Lys										: :		
٠.			· .	270)							· ••	:	٠, .,	ı 1 •	
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															ctcctc	1110

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NEDOCID - WO 011266042 I -

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Tyr	Tyr	Phe	Leu	Ĺys	Arg	Tyr	Phe	Gly	Ser	Thr	Val	Ala	Phe	Leu	Asn
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Leu	Trp	Thr	Ser	Leu	Phe	Leu	Gly	Ser	Gly	Val	Val	Ala	Gly	Gln	Ala
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Val	Pro	Lys	Leu	Pro	Lys	Lys	Cys	Leu	Ala	Leu	Ala	Met	Leu	Trp	Ile
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Ile	Ala	Ser	Ser	Val	Leu	Lys	Val	Ser	Ile	Leu	Ser	Phe	Ile	Ser	Leu
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Thr	Gly	Val	Val	Phe	Leu	Ile	Arg	Gly	Lys	Lys	Glu	Asn	Val	Glu	Arg
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Phe	Gln	Asn	Ala	Phe	Asp	Ala	Glu	Leu	Pro	Asp	Ile	Ser	His	Leu	Ile
÷	1	195			•		200			. :		205			· ./ 3
Gln	Ala	Ile	Phe	Gln	Gly	Tyr	Phe	Ala	Tyr	Ser	Gly	Glu	Leu	Lys	Lys
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Pro	Arg	Thr	Thr	Ile	Pro	Lys	Cys	Ile	Phe	Thr	Ala	Leu	Pro	Leu	Val
225	٠	•	٠.		230			• •		235			٠,		240
Thr	Val	Val	Tyr	Leu	Leu	Val	Asn	Ile	Ser	Tyr	Leu	Thr	Val	Leu	Thr
:	٠	•	•	245	•	. 3		. :,	250			.: .		255	· .

Pro	Arg	Glu	Ile	Leu	Ser	Ser	Asp	Ala	Val	Ala	Ile	Thr	Trp	Ala	Asp
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Arg	Ala	Phe	Pro	Ser	Leu	Ala	Trp	Ile	Met	Pro	Phe	Ala	Ile	Ser	Thr
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1		5	• .	· :	ı		10	;	•			15	• • •
Cys Leu Ser	Ala	Arg	Asp	Gly	Ser	Årg	Met	Leu	Leu	Leu	Leu	Leu	Leu
to the way of	20		•	;		25		٠.	٠٠.	•.	30	1	: ., ·
Leu Gly Ser	Gly	Gln	Gly	Pro	Gln	Gln	Val	Gly	Ala	Gly	Gln	Thr	Phe
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Glu Tyr Leu	Lys	Arg	Glu	His	Ser	Leu	Ser	Lys	Pro	Tyr	Gln	Gly	Val
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Gly Thr Gly	Ser	Ser	Ser	Leu	Trp	Asn	Leu	Met	Gly	Asn	Ala	Met	Val
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Met Thr Gln	Tyr	Ile	Arg	Leu	Thr	Pro	Asp	Met	Gln	Ser	Lys	Gln	Gly
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Ala Leu Trp	Asn	Arg	Val	Pro	Cys	Phe	Leu	Arg	Asp	Trp	Glu	Leu	Gln
	100					105				٠	110		. •
Val His Phe	Lys	Ile	His	Gly	Gln	Gly	Lys	Lys	Asn	Leu	His	Gly	Asp
115				•	120					125	;		:
Gly Leu Ala	Ile	Trp	Tyr	Thr	Lys	Asp	Arg	Met	Gln	Pro	Gly	Pro	Val
130				135	;				140	•	•	•	. :
Phe Gly Asn	Met	Asp	Lys	Phe	Val	Gly	Leu	Gly	Val	Phe	Val	Asp	Thr
145			150)				155	;				160
Tyr Pro Asn	Glu	Glu	Lys	Glr	ı Glm	Glu	Arg	(Val	Phe	Pro	Туг		
		165	5				170)				175	; ** 🕹
Ala Met Val	. Asn	ı Ası	ı Gly	r Sei	r Leu	ı Sei	Туг	. Asp	His	s Glu			
	180)				18	5			.* .	190) ' '	• •
Arg Pro Thi	Gli	ı Lei	u G13	/ G1:	y Cys	s Thi	r Ala	a Ile	e Val	l Ar	g Ası	n Lei	His
198	5	(; ,	• • • •		200	ο,	. ,-		•	20	5 · "	1 1 13	(- 260

Tyr Asp Thr Phe Leu Val Ile Arg Tyr Val Lys Arg His Leu	Thr Ile
210 215 220	
Met Met Asp Ile Asp Gly Lys His Glu Trp Arg Asp Cys Ile	Glu Val
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Pro Gly Val Arg Leu Pro Arg Gly Tyr Tyr Phe Gly Thr Ser	Ser Ile
245 250	255
Thr Gly Asp Leu Ser Asp Asn His Asp Val Ile Ser Leu Lys	Leu Phe
260 265 270	
Glu Leu Thr Val Glu Arg Thr Pro Glu Glu Glu Lys Leu His	Arg Asp
275 280 285	
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305 310 315	320
Ser Leu Val Phe Ser Val Phe Ala Ile Val Ile Gly Ile Ile	Leu Tyr
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Met Glu Leu Leu Gln Val Thr Ile Leu Phe Leu Leu Pro Ser	Ile Cys

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Ser	Ser	Asn	Ser	Thr	Gly	Val	Leu	Glu	Ala	Ala	Asn	Asn	Ser	Leu	Val
		٠,	·20	. •			-	25					30	•••	74. · · · ·
Val	Thr	Thr	Thr	Lys	Pro	Ser	Ile	Thr	Thr	Pro	Asn	Thr	Glu	Ser	Leu
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Lys	Asn	Asp	Ser	Ile	Ile	Ser	Asn	Val	Thr	Val	Thr	Ser	Val	Thr	Leu
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Pro	Asn	Ala	Val	Ser	Thr	Leu	Gln	Ser	Ser	Lys	Pro	Lys	Thr	Glu	Thr
	. •	115	5		•		120	i .				125	5		es de la
Glr	Ser	Ser	r Ile	. Lys	Thr	Thr	Glu	Ile	Pro	Gly	Ser	· Val	Leu	ı Glr	Pro
	130)				135					140	,	٠	• • •	
Asp	Ala	a Sei	r Pro	Ser	Lys	Thr	Gly	Thr	Leu	Thi	Sei	r Ile	e Pro	Va]	Thr
145	5				150)				158	5				160
116	e Pro	o Gl	u Ası	n Thi	r Sei	Glr	ı Ser	Gln	Val	. 11	e Gly	y Thi	r Gl	u Gl	y Gly
				16	5				170)				17	5 👯 😘
Ly	s As	n Al	a Se	r Th	r Se	r Ala	a Thi	r Ser	Arg	g Se	r Ty	r Se			e Ile
			18	0				185	5			•	19	0	+ 54 E
Le	u Pr	o Va	l Va	1 11	e Al	a Le	u Il	e Val	l 11e	e Th	r Le	u Se	r Va	1 Ph	e Val
٠.		19	5		J++,		. 20	0	٤	: -/	. ;; .	20	5	٠: ٠	S 1 360

Leu	Val	Gly	Leu	Tyr	Arg	Met	Cys	Trp	Lys	Ala	Asp	Pro	Gly	Thr	Pro
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Leu	Thr	Val	Lys	Thr	Ile	Ser	His	Glu	Ser	Gly	Glu	His	Ser	Ala	Gln
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Cys	Gln	Pro	Gly	Ala	Glu	Asn	Ala	Phe	Lys	Val	Arg	Leu	Ser	Ile	Arg
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Glu	Ala	Thr	Glu	Ile	Ser	His	Val	Leu	Leu	Cys	Asn	Val	Thr	Gln	Arg
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Val	Ser	Phe	Trp	Phe	Va1	Val	Thr	Asp	Pro	Ser	Lys	Asn	His	Thr	Leu

	i i	.•	•	85	÷		٠		90			•		95	• •
Pro	Ala	Val	Glu	Val	Gln	Ser	Ala	Ile	Arg	Met	Asn	Lys	Asn	Arg	Ile
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Asn	Asn	Ala	Phe	Phe	Leu	Asn	Asp	Gln	Thr	Leu	Glu	Phe	Leu	Lys	Ile
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Pro	Ser	Thr	Leu	Ala	Pro	Pro	Met	Asp	Pro	Ser	Val	Pro	Ile	Trp	Ile
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Ile	Ile	Phe	Gly	Val	Ile	Phe	Cys	Ile	Ile	Ile	Val	Ala	Ile	Ala	Leu
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Ser	Glu	Val	Asp	Asp	Ala	Glu	Asp	Lys	Cys	Glu	Asn	Met	Ile	Thr	Ile
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Ası	n Asp	Ala	. Phe	e Met	: Thr	Glu	. Asp	Glu	Arg	Leu	Thr	Pro	Let	l	
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															5 1 1

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His	Cys	Leu	Thr	Thr	Asp	Trp	Val	His	Leu	Trp	Tyr	Ile	Trp	Leu	Leu
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Leu	Gln	Ser	Thr	Ile	Thr	Ser	Leu	Gln	Ser	Val	Phe	Gly	Pro	Ala	Ala
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Arg	Arg	Ile	Leu	Ala	Val	Ala	His	Ser	His	Ser	Ser	Leu	Gly	Gln	Leu
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Pro	Ser	Ser	Leu	Asp	Thr	Leu	Pro	Gly	Tyr	Glu	Glu	Ala	Leu	His	Met
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Ser	Arg	Phe	Thr	Val	Ala	Met	Cys	Gly	Gln	Lys	Ala	Pro	Asp	Leu	Pro
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Lys	Ser	Ile	Leu	Ser	Ser	Lys	Pro	Ala	Ile	Gly	Ser	Lys	Ala	Val	Asn
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Tyr	Ser	Ser	Thr	Gly	Ser	Ser	Lys	Ser	Phe	Cys	Ser	Cys	Val	Pro	Cys
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Glu	Gly	Thr	Ala	Asp	Ala	Ser	Phe	Val	Thr	Cys	Pro	Thr	Cys	Gln	Gly
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Ser	G1 ₃	, Lys	Ile	Pro	Gln	Glu	Leu	Glu	Lys	Gln	Leu	Val	Ala	Leu	Ile
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Pro	Ty	r Gly	/ Asp	Gln	Arg	Leu	Lys	Pro	Lys	His	Thr	Lys	Leu	Phe	Val
		÷		85					90		•			95	
Phe	Le	u Ala	a Val	Leu	Ile	Cys	Leu	Val	Thr	Ser	Ser	Phe	Ile	Val	Phe
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Phe	Le	u Pho	e Pro	Arg	g Ser	· Val	Ile	. Val	Gln	Pro	Ala	Gly	Leu	. Asn	Ser
-	:	· 11	5	-			120) ·		• • •		125	5	•	
Sei	. Th	r Va	l Ala	a Phe	e Asp	Glu	ı Ala	a Asp	Ile	e Tyi	r Lei	ı Ası	ı Ile	Thr	Asn
	13	0				135	5				140) -		t ·	e de la company
Ile	e Le	u As	n Il	e Sei	r Ası	n Gly	, Ası	n Tyi	r Tyi	r Pr	o Ile	e Me	t Va	l Thi	Gln
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Le	u Th	ır Le	u Gl	u Va	l Le	u Hi:	s Le	u Sei	r Le	u Va	l Va	1 G1	y Gl	n Va	l Ser-
				16					17						5 .i.

Asn Asn Leu Leu His Ile Gly Pro Leu Ala Ser Glu Glr	Met Phe
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Tyr Ala Val Ala Thr Lys Ile Arg Asp Glu Asn Thr Tyr Lys	s Ile Cys
195 200 205	
Thr Trp Leu Glu Ile Lys Val His His Val Leu Leu His Ile	Gln Gly
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Thr Ala Ala Ala Leu Ala Thr Gly Ala Cys Ile Val Gly Ile	

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Asn	Arg	Arg	Ala	Gln	Glu	Leu	Val	Arg	Met	Asp	Ser	Asn	Ile	Gln	Gly	
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Ile	Glu	Asn	Pro	Gly	Phe	Glu	Ala	Ser	Pro	Pro	Ala	Gln	Gly	Ile	Pro	
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Glu	Ala	Lys	Val	Arg	His	Pro	Leu	Ser	Tyr	Val	Ala	Gln	Arg	Gln	Pro	
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Ser	Glu	Ser	Gly	Arg	His	Leu	Leu	Ser	Glu	Pro	Ser	Thr	Pro	Leu	Ser	
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;	1 -			٠ (5				: 10			•		15	5 - 2	٠.
Lei	u Lei	u Gl	y Vai	l Ala	a Ala	a Sei	r Lei	ц Су:	s Val	l Ar	g Cy:	s Sei	r Arı	g Pro	Gly	
•		:	· 9	n ·				. 2	5			• .	- 3()		٠, .

Ala	Lys	Arg	Ser	Glu	Lys	Ile	Tyr	Gln	Gln	Arg	Ser	Leu	Arg	Glu	Asp
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Gln	Gln	Ser	Phe	Thr	Gly	Ser	Arg	Thr	Tyr	Ser	Leu	Val	Gly	Gln	Ala
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Leu	Gln	Phe	Tyr	Pro	Ser	Leu	Glu	Asp	Pro	Ala	Ser	Ser	Arg	Tyr	Gln
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Lys	Thr	Thr	Glu	Thr	Gly	Ala	Gln	Gln	Glu	Gly	Ile	Gly	Gly	Leu	Cys
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Arg	Gly	Asp	Leu	Ser	Leu	Ser	Leu	Ala	Leu	Lys	Thr	Gly	Pro	Thr	Ser
,	•			165					170					175	
Gly	Leu	Cys	Pro	Ser	Ala	Ser	Pro	Glu	Glu	Asp	Glu	Glu	Ser	Glu	Asp
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Tyr	Gln	Asn	Ser	Ala	Ser	Ile	His	Gln	Trp	Arg	Glu	Ser	Arg	Lys	Val
	34 J.	195	· ·	•			200	•			٠,	205	, .	, •	··
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٠.	[•] 210	·	ı	y 1.	۲.	215	•				. 220		,.	٠.,	•
Asp	G1u	G1u	Asp	Gly	Glu	Pro	Asp	Tyr	· Val	Asn	Gly	Gli	ı Val	·Ala	Ala

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															Asn

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Glu Leu (Glu Lys	Gln Let	ı Tyr Se	r Cys	Ile Ala	Leu Lys	Val Thr	Ala
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Asn Gln N	Met Glu	Met Gl	ı His Se	r Leu	Ile Leu	Asn Asn	Leu Lys	Thr
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Gly Ala	Gln Ly	s Ala Al	la Leu V	al Le	u Leu Se	r Ala Cy	s Leu Va	l Thr
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Leu	Pro	Gln	Gln	Thr	Ala	Asp	Arg	Ala	Gly	Ile	Lys	Asp	Aŗg	Val	Tyr.
225.	21.	÷ 1.	,	÷ _	230			•		235			: .	٠	240
Ser.	Asn.	Ser	Ile	Tyr	Glu	Leu	Leu	Glu	Asn	Gly	Gln	Arg	Asn	Leu	Gln

or and a second of the second

154/307

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156/307

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240

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162/307

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attgtaattt atatagaatt ttaaaaactct tcaattaca	atg gat aga	ggg gag	114
to a contract of the second	Met Asp Arg	g Gly Glu	
engan kanalan di kacamatan kanalan kanalan da kanalan kanalan kanalan kanalan kanalan kanalan kanalan kanalan Kanalan kanalan kanala	1		

aaa	ata	cag	ctc	aag	aga	gtg	ttt	gga	tat	tgg	tgg	ggc	aca	agt	ttt	162
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Ala	Gly	Cys	Ala	Ile	Leu	Ala	Met	Thr	Ser	Thr	Leu	Cys	Ser	Ala	Glu	
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	;	120	٠, ٦		٠.	٠.	125			-		130			-	
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Leu	Lys	Val	Ser	Ile	Leu	Ser	Phe	Ile	Ser	Leu	Thr	Gly	Val	Val	Phe	
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Asp	Ala	Glu	ı Leu	Pro	Asp	Ile	Ser	His	Leu	Ile	Glr	Ala	ı Ile	Phe	Gln	
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gga	a tai	t tti	gca	ta1	t tca	a ggg	gag	ctg	g aag	aag	cco	aga	a aca	a aca	aatt	786
Gl	у Туз	r Phe	e Ala	Туз	r Sei	r Gly	Glu	ı Lev	ı Lys	Lys	Pro	Ar	g Thi	r Thi	r Ile	
	21	5				220)				22	5		٠.	• •	
cc	c aa	a tg	c ata	a tt	t ac	t gc	g tta	a cc	t ctg	g gtg	g ac	t gt	a gt	t ta	t tta	834
Pr	o Ly	s Cy	s Ile	e Ph	e Th	r Ala	a Lei	u Pr	o Lei	ι Val	l Th	r Va	l Va	1 Ty	r Leu	
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Lė	u Va	ıl As	n Il	e Se	r Ty									u Il	e Leu	
									25						iO 1 /	
to	t to	a ga	it go	t gt	a go	t at	c ac	a tg	g gc	t ga	t cg	ga go	t tt	t co	c tca	930
c.	·c.	- · · · · ·		o Vis	.1 Δ1	11 د	e Th	r Tr	n Al	a As	D A	g Al	la Pi	ne Pi	o Ser	

			265	i				270)				275	;		
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Leu	Ala	Trp	Ile	Met	Pro	Phe	Ala	Ile	Ser	Thr	Ser	Leu	Phe	Ser	Asn	
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Gly	Ser	Leu	Trp	Ser	Ile	Leu	Leu	Met	Ile	Gly	Ile	Leu	Arg	Arg	Arg	
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Trp	Glņ	Gln	Trp	Arg	Arg	Cys	Leu	Ser	Ala	Arg	Asp	Gly	Ser	Arg	Met	
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Leu	Leu	Leu	Leu	Leu	Leu	Leu	Gly	Ser	Gly	G1n	G1y	Pro	Gln	Gln	Val	
5			. 30		:			35				-	40			
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Gly	Ala	Gly	Gln	Thr	Phe	Glu	Tyr	Leu	Lys	Arg	Glu	His	Ser	Leu	Ser	
		45	٠ .	· • · · ·			· 50				٠. ،	- 55		wile or	بار.	
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Lys	Pro	Tyr	Gln	Gly	Val	Gly	Thr	Gly	Ser	Ser	Sei	Leu	Trp	Asr	ı Leu	
	60	•	y.		•	65	,	•	٠.	٠.	70)	1.		at a	
atg	ggc	aat	gcc	ate	gtg	g ate	gaco	c cas	g tai	t ate	c cg	cicti	t acc	cca	a gat	291
															o Asp	

75					80					85	;			•	. 90	
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Phe Tyr

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Ser Asn Ser	Thr Gly V	al Leu Glu	Ala Ala Asn	Asn Ser Leu	Val Val
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Thr Thr Thr	Lys Pro S	Ser Ile Thr	Thr Pro Asr	Thr Glu Ser	Leu Gln
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Lys Asn Val	Val Thr F	ro Thr Thr	Gly Thr Th	r Pro Lys Gly	Thr Ile
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Thr Asn Glu	Leu Leu l	Lys Met Sei	Leu Met Se	r Thr Ala Th	r Phe Leu
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Ser	Ser	Ile	Lys	Thr	Thr	Glu	Ile	Pro	Gly	Ser	Val	Leu	Gln	Pro	Asp	
130					135					140					145	
gca	tca	cct	tct	aaa	act	ggt	aca	tta	acc	tca	ata	cca	gtt	aca	att	537
Ala	Ser	Pro	Ser	Lys	Thr	Gly	Thr	Leu	Thr	Ser	Ile	Pro	Val	Thr	Ile	
				150					155					160	<i>t</i> .	
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Pro	Glu	Asn	Thr	Ser	G1n	Ser	Gln	Val	Ile	Gly	Thr	Glu	Gly	Gly.	Lys	
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Asn	Ala	Ser	Thr	Ser	Ala [.]	Thr.	Ser	Arg	Ser	Tyr	Ser	Ser	Ile	Ile	Leu	
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Pro	Val	Val	Ile	Ala	Leu	Ile	Val	Ile	Thr	Leu	Ser	Val	Phe	Val	Leu .	
	195					200					205					
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Asn Gly Asn Asp Gln Pro Gln Ser Asp Lys Glu Ser Val Lys Leu Leu	
230 235 240	
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Thr Val Lys Thr Ile Ser His Glu Ser Gly Glu His Ser Ala Gln Gly	
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Lys Thr Lys Asn	
260	
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State - 15 12 22 21

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act gcc att	cat gct	gaa ctc	tgt caa	cca ggt	gca gaa	aat gct	ttt 100
Thr Ala Ile	His Ala	Glu Leu	Cys Gln	Pro Gly	Ala Glu	Asn Ala	Phe
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aaa _. gtg aga	ctt agt	atc aga	aca gct	ctg gga	gat aaa	gca tat	gcc 148
Lys Val Arg	Leu Ser	Ile Arg	Thr Ala	Leu Gly	Asp Lys	Ala Tyr	Ala
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tgg gat acc	aat gaa	gaa tac	ctc ttc	aaa gcg	atg gta	gct ttc	tcc 196
Trp Asp Thr	Asn Glu	Glu Tyr	Leu Phe	Lys Ala	Met Val	Ala Phe	Ser .
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atg aga aaa	gtt ccc	aac aga	gaa gca	aca gaa	att tcc	cat gtc	cta 244
Met Arg Lys	Val Pro	Asn Arg	Glu Ala	Thr Glu	Ile Ser	His Val	Leu
. 60			65		. 70		
ctt tgc aat	gta acc	cag agg	gta tca	ttc.tgg	ttt gtg	gtt aca	gac 292
Leu Cys Asn	Val Thr	Gln Arg	Val Ser	Phe Trp	Phe Val	Val Thr	Asp
75 ; • .	· · · ·	- 80			85	• ,	• •
cct tca aaa	aat cac	acc ctt	cct gct	gtt gag	gtg caa	tca gcc	ata 340
Pro Ser Lys	Asn His	Thr Leu	Pro Ala	Val Glu	Val Gln	Ser Ala	Ile
90% - 144	• • • •	95		100	*****	· • • •	105.

aga	atg	aac	aag	aac	cgg	atc	aac	aat	gcc	ttc	ttt	cta	aat	gac	caa	3	388
Arg	Met	Asn	Lys	Asn	Arg	Ile	Asn	Asn	Ala	Phe	Phe	Leu	Asn	Asp	Gln		•
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Thr	Leu	Glu	Phe	Leu	Lys	Ile	Pro	Ser	Thr	Leu	Ala	Pro	Pro	Met	Asp		
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Pro	Ser	Val	Pro	Ile	Trp	Ile	Ile	Ile	Phe	Gly	Val	Ile	Phe	Cys	Ile		
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Ile	Ile	Val	Ala	Ile	Ala	Leu	Leu	Ile	Leu	Ser	Gly	Ile	Trp	Glr	Arg		
	155	;				160)				165	Ì	*				
aga	aga	aag	g aad	aaa	. gaa	cca	tct	. gaa	gtg	gat	gac	gct	gaa	gat	aag		580
Arg	Arg	y Lys	s Ası	n Lys	Glu	Pro	Ser	Glu	Val	. Asp	Asp	Ala	a Glu	ı Ası) Lys		
170)				179	5				180)				185	ı	
tgt	ga:	a aa	c at	g ato	aca	a at	t gaa	a aat	ggo	ato	ccc	tc.	t ga	t cc	c ctg		628
Cys	Gl:	u As	n Me	t Ile	e Thi	r Il	e Glu	ı Asr	Gly	y I16	e Pro	o Se	r As	p Pr	o Leu	ļ	
		•	. ,	190)				19	5				20	0	•	
ga	at	g aa	g gg	a ggi	g ca	t at	t aa	t ga	t gc	c tt	c at	g ac	a ga	g ga	t gag	3	676
As	р Ме	t Ly	s Gl	y Gl											p Glu		
	. <i>:</i>	••	20	5				21	0 -			-	21	5	:	: .	
															acat		730
															\$ 4 9		
tt	øtti	tote	t et	gacte	ctg	agca	atcct	ga a	atac	caag	ga go	aga	tcata	a ta	ttttg	ttt	790

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• • •	Met Gl	y Val Arg V	al His Val	Val Ala Ala	Ser Ala	
3 40 5 40 5	1 .		5	10	· , , , , ,	
ctg ctg tat	ttc atc ct	g ctt tct g	gg acg aga	tgt gag gaa	aac tgt	158

Leu Leu Tyr Phe Ile Leu Leu Ser Gly Thr Arg Cys Glu Glu Asn Cys

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Gly	Asn	Pro	Glu	His	Cys	Leu	Thr	Thr	Asp	Trp	Val	His	Leu	Trp	Tyr	
	30		· .	•		35					40					
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Ile	Trp	Leu	Leu	Val	Val	Ile	Gly	Ala	Leu	Leu	Leu	Leu	Cys	Gly	Leu	
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His	Asp	Ser	Thr	Leu	Gln	Ser	Thr	Ile	Thr	Ser	Leu	Gln	Ser	Val	Phe ·	
		95					100					105			• • •	
ggc	cct	gca	gct	cgg	agg	atc	ctg	gct	gtg	gct	cac	tcc	cac	agc	tcc··	446
Gly	Pro	Ala	Ala	Arg	Arg	Ile	Leu	Ala	Val	Ala	His	Ser	His	Ser	Ser	
	110					115					120				e cherry	
ctg	ggc	cag	ctg	ccc	tcc	tct	ttg	gac	·acc	ctc	cca	ggg	tat	gaa	gaa	494
Leu	Gly	Gln	Leu	Pro	Ser	Ser	Leu	Asp	Thr	Leu	Pro	Gly	Tyr	Glu	·Glu·	
125	;-• ·		<i>.</i>		130	,	. .	. ;	*	135					140	
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Ala	Leu	His	Met	Ser	Arg	Phe	Thr	Val	Ala	Met	Cys	Gly	Glr	Lys	s-Ala-	
	•	• •		-145	5	. .	٠. ,	F	· 150)				155	5 ia 16%.	

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Pro Asp Leu Pro Pro Val	Pro Glu Glu Lys Gln	Leu Pro Pro Thr Glu	
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Lys Glu Ser Thr Arg Ile	Val Asp Ser Trp Asn		
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THE SHARE SHEET STORES

286

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Ser	Ile	Leu	Ser	Ser	Lys	Pro	Ala	Ile	Gly	Ser	Lys	Ala	Val	Asn	Tyr	
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Ser	Ser	Thr	Gly	Ser	Ser	Lys	Ser	Phe	Cys	Ser	Cys	Val	Pro	Cys	Glu	
•	35	•		*		.40			•		45					
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Gly	Lys	Ile	Pro	Gln	Glu	Leu	Glu	Lys	Gln	Leu	Val	Ala	Leu	Ile	Pro	
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tat	ggg	gac	cag	agg	ctg	aag	ссс	aag	cac	acg	aag	ctc	ttt	gtg	ttc	526
Tyr	Gly	Asp	Gln	Arg	Leu	Lys	Pro	Lys	His	Thr	Lys	Leu	Phe	Val	Phe	
٠٠.	· ·- ;	,	· 85			•		90		,			95	. ,		
ctg	gcc	gtg	ctc	atc	tgc	ctg	gtg	acc	tcc	tcc	ttc	atc	gtc	ttt	-ttc	574
Leu	Ala	Val	Leu	Ile	Cys	Leu	Val	Thr	Ser	Ser	Phe	Ile	Val	Phe	Phe	
•••		100		ì		• .	105	٠.				110		.	, .	
ctg	ttt	ccc	cgg	tcc	gtc	att	gtg	cag	cct	gca	ggc	ctc	aac	tcc	tcc	622
Leu	Phe	Pro	Arg	Ser	Val	Ile	Val	Gln	Pro	Ala	Gly	Leu	Asn	Ser	Ser	
•	·115			`		120	,.				125	•		•.		
aca	gtg	gcc	ttt	gat	gag	gct	gat	atc	tac	ctc	aac	ata,	acg	aat	atc	670
Thr	Val	A16	Dho	Acr	G1.	41.	100	Tla	T	I ou	10=	Tic	The	A 0.5	T1.	

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Leu Asn Ile Ser Asn Gly	Asn Tyr Tyr Pro	Ile Met Val Thr Gln Leu	
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Thr Leu Glu Val Leu His	Leu Ser Leu Val	Val Gly Gln Val Ser Asn	
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Asn Leu Leu Leu His Ile	Gly Pro Leu Ala	Ser Glu Gln Met Phe Tyr	
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gca gta gct acc aag ata	cgg gat gaa aac	aca tac aaa atc tgt acc	862
Ala Val Ala Thr Lys Ile	Arg Asp Glu Asn	Thr Tyr Lys Ile Cys Thr	
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Leu Thr Cys Ser Tyr Leu	Ser His Ser Glu	Gln Leu Val Phe Gln Ser	
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Tyr Glu Tyr Val Asp Cys	Arg Gly Asn Ala	a Ser Val Pro His Gln Leu	
245	··· ·· 250 ··	255	
acc cct cac cca cca tga	cctgtc tgctgtcc	ct gtactccagg cacctgcaac	1060
Thr Pro His Pro Pro			
260	logova se som	. In the second section of the second	

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Met Gly Val Pro

non operation of the company on the many the contract and are

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5	٠,; ,	.:			10	٠,	•	•		15		•	:		20	
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Asp Pro Glu	Ser Il		ly Gly	Tyr Ala	Glu Phe	Leu Ty	r Gln Ile
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Gly Leu Leu			ln Lvs	Lvs Tyr	Phe Glm	Lys Gl	n Cys His
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•			Leu Tyr			e Leu S	er Leu Pro
41. · · · ·		25	<u>*</u> .	33			335
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Phe Th	ur I	le	Phe	Lys	Val	Ala	Gly	Tyr	Ile	Gln	Ala	Cys	Arg	Gly	Leu
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Met II	le A	lla	Ala	Val	Ser	Leu	Gly	Phe	Phe	Gly	Ser	Ile	Phe	Ala	Leu
	-	• •		85	•		•		90	•				9 5	·
Phe G	ly M	let	Lys	Cys	Thr	Lys	Val	Gly	Gly	Ser	Asp	Lys	Ala	Lys	Ala
			100					105	•				110		\$ - 4
Lys I	le A	Ala	Cys	Leu	Ala	Gly	Ile	Val	Phe	Ile	Leu	Ser	Gly	Leu	Cys
]	115	•			٠	120		•		-	125	1	•	a Error
Ser Mo	et 1	Thr	Gly	Cys	Ser	Leu	Tyr	Ala	Asn	Lys	Ile	Thr	Thr	Glu	Phe
1:	30					135				•	140			•	
Phe A	sp I	Pro	Leu	Phe	Val	Glu	Gln	Lys	Tyr	Glu	Leu	Gly	Ala	Ala	Leu
145					150	,				155					160
Phe I	le (Gly	Trp	Ala	Gly	Ala	Ser	Leu	Cys	Ile	Ile	Gly	Gly	Val [*]	Ile
				165					170					175	
Phe C	ys 1	Phe	Ser	Ile	Ser	Asp	Asn	Asn	Lys	Thr	Pro	Arg	Tyr	Thr	Tyr
			180					185					190		
Asn G	ly .	Ala	Thr	Ser	Val	Met	Ser	Ser	Arg	Thr	Lys	Tyr	His	Gly	Gly
		195					200		·			205		•	
Glu A	sp	Phe	Lys	Thr	Thr	Asn	Pro	Ser	Lys	Gln	Phe	Asp	Lys	Asn	Ala:
2	10	1		•		215	•		•	••	220	. •	, .	;	PS + 1 +
Tyr V	al												•		
225					٠.		•	. .	• *	• •				. 1.	· 1

<21	l> 30	05					-								
<212	2>_PI	RT .	,				i					i			
<213	3> Ho) O O O	sapie	ens											
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Met	Gly	Ile	Gln	Thr	Ser	Pro	Val	Leu	Leu	Ala	Ser	Leu	Gly	Val	Gly
1				5					10					. 15	
Leu	Val	Thr	Leu	Leu	Gly	Leu	Ala	Val	Gly	Ser	Tyr	Leu	Val	Arg	Arg
			20					25					30		
Ser	Arg	Arg	Pro	Gln	Val	Thr	Leu	Leu	Asp	Pro	Asn	Glu	Lys	Tyr	Leu
		35					40					45			
Leu	Arg	Leu	Leu	Asp	Lys	Thr	Thr	Val	Ser	His	Asn	Thr	Lys	Arg	Phe
	50					55					60				
Arg	Phe	Ala	Leu	Pro	Thr	Ala	His	His	Thr	Leu	Gly	Leu	Pro	Val	Gly
65					70					75					80
Lys	His	Ile	Tyr	Leu	Ser	Thr	Arg	Ile	Asp	Gly	Ser	Leu	Val	Ile	Arg
1	-•	•.		85					90					. 95	
Pro	Tyr	Thr	Pro	Val	Thr	Ser	Asp	Glu	Asp	Gln	Gly	Tyr	Val	Asp	Leu
			100					105					110		
Val	Ile	Lys	Val	Tyr	Leu	Lys	Gly	Val	His	Pro	Lys	Phe	Pro	Glu	Gly
		115					120					125			
Gly	Lys	Met	Ser	Gln	Tyr	Leu	Asp	Ser	Leu	Lys	Val	Gly	Asp	Val	Val
	130					135					140				٠,٠
Glu	Phe	Arg	Gly	Pro	Ser	Gly	Leu	Leu	Thr	Tyr	Thr	Gly	Lys	Gly	His
145					150					155	:				160
Phe	Asn	Ile	Gln	Pro	Asn	Lvs	l.vs	Ser	Pro	Pro	Glu	Pro	Arø	Val.	Ala

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		165					170					175	٠ :	
Lys Lys Leu	Gly	Met	Ile	Ala	Gly	Gly	Thr	Gly	Ile	Thr	Pro	Met	Leu	
	180					185					190	•	N.S.	,
Gln Leu Ile	Arg	Ala	Ile	Leu	Lys	Val	Pro	Glu	Asp	Pro	Thr	Gln	Cys	
· · · · · · · · · · · 195			. •		200		,			205		.: •	,	
Phe Leu Leu	Phe	Ala	Asn	Gln	Thr	Glu	Lys	Asp	Ile	Ile	Leu	Arg	Glu	
210				215					220				,	
Asp Leu Glu	Glu	Leu	Gln	Ala	Arg	Tyr	Pro	Asn	Arg	Phe	Lys	Leu	Trp	
225		4	230	,				235					240	
Phe Thr Leu	Asp	His	Pro	Pro	Lys	Asp	Trp	Ala	Tyr	Ser	Lys	Gly	Phe	
		245					250				٠.	255	1. 1	
Val Thr Ala	Asp	Met	Ile	Arg	Glu	His	Leu	Pro	Ala	Pro	Gly	Asp	Asp	
	260	١				265		•			270	· `.	á	
Val Leu Val	Leu	Leu	Cys	Gly	Pro	Pro	Pro	Met	Val	G1n	Leu	Ala	Cys	
275					280					285	; ,			
His Pro Asn	Leu	ı Asp	Lys	Leu	Gly	Tyr	Ser	Gln	Lys	Met	. Arg	, Phe	Thr	
290			,	295					300			•		٠.
Tyr														
305					4	,		,	•				1 -	. 1
<210> 94					÷			,				. :		
<211> 227												١		
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<213> Homo	sap	iens											÷.	:
<400> 94 ·	<u>.</u>	:	'	7 :	,					.: •) ·:	· . :•	•	·

Me	t Gl	y Tr	p Thi	r Mei	t Arg	, Lei	u Va	1 Thi	r Ala	a Ala	Lei	ı Lei	ı Le	u Gl	y Leu
	l,	•		8	5		. •		10)			,	1	5 .
Me	t Me	t Va	l Val	l Thr	Gly	Asp	Glu	ı Asp	Glu	ı Asr	Ser	Pro	Су	s Ala	His
			20)				25	j				36) .	. •
Glu	ı Ala	a Lei	ı Lev	ı Asp	Glu	Asp	Thr	- Leu	Phe	e Cys	Glr	Gly	Lei	ı Glu	ı Val
		3	5				40)				45	j		
Phe	Туг	Pro	Glu	ı Leu	Gly	Asn	Ile	Gly	Cys	Lys	Val	Val	Pro	Asp	Cys
	50)				55	•				60	,			
Asn	Asn	туг	Arg	Gln	Lys	Ile	Thr	Ser	Trp	Met	Glu	Pro	Ile	· Val	Lys
65					70					75					80
Phe	Pro	Gly	Ala	Val	Asp	Gly	Ala	Thr	Tyr	Ile	Leu	Val	Met	Val	Asp
	٠.,			85					90					95	•
Pro	Λsp	Ala	Pro	Ser	Arg	Ala	Glu	Pro	Arg	Gln	Arg	Phe	Trp	Arg	His
			100					105					110		
Trp	Leu	Val	Thr	Asp	Ile	Lys	Gly	Ala	Asp	Leu	Lys	Lys	Gly	Lys	Ile
	:	115					120					125		٠.	
Gln	Gly	Gln	Glu	Leu	Ser	Ala	Tyr	Gln	Ala	Pro	Ser	Pro	Pro	Ala	His
	130					135					140				
Ser	Gly	Phe	His	Arg	Tyr	Gln	Phe	Phe	Val	Tyr	Leu	Gin	Glu	Gly	Lys
145					150					155				;	160
											Arg	Gly	Ser	Trp	Lys -
								•							*
								His							
Thr	Gln	Phe	Met	Thr	Gln .	Asn	Tyr	Gln	Λsp	Ser	Pro	Thr	Leu	Gln	Ala

195 200 205 Pro Arg Glu Arg Ala Ser Glu Pro Lys His Lys Asn Gln Ala Glu Ile 210 215 220 Ala Ala Cys **225** <210> 95 <211> 441 <212> PRT <213> Homo sapiens <400> 95 Mct Ala Ile His Lys Ala Leu Val Met Cys Leu Gly Leu Pro Leu Phe 15 1 10 5 Leu Phe Pro Gly Ala Trp Ala Gln Gly His Val Pro Pro Gly Cys Ser 30 20 25 Gln Gly Leu Asn Pro Leu Tyr Tyr Asn Leu Cys Asp Arg Ser Gly Ala 40 45 Trp Gly Ile Val Leu Glu Ala Val Ala Gly Ala Gly Ile Val Thr Thr 60 50 55 Phc Val Leu Thr Ile Ile Leu Val Ala Ser Leu Pro Phe Val Gln Asp 65 75 75 80 Thr Lys Lys Arg Ser Leu Leu Gly Thr Gln Val Phe Phe Leu Leu Gly 85 90 95 95 Thr Leu Gly Leu Phe Cys Leu Val Phe Ala Cys Val Val Lys Pro Asp ... 100 means of 105 means to 110 means of

Phe	Ser	Thi	Cys	Ala	Ser	Arg	Arg	Phe	Leu	Phe	Gly	Val	Leu	Phe	Ala
	• •	118	5		· ·		120)				125	,		
Ile	Cys	Phe	Ser	Cys	Leu	Ala	Ala	His	Val	Phe	Ala	Leu	Asn	Phe	Leu
	130					135	ı				140		,		
Ala	Arg	Lys	Asn	His	Gly	Pro	Arg	Gly	Trp	Val	Ile	Phe	Thr	Val	Ala
145	•				150					155					160
Leu	Leu	Leu	Thr	Leu	Val	Glu	Val	.Ile	Ile	Asn	Thr	Glu	Trp	Leu	Ile
				165					170					175	
Ile	Thr	Leu	Val	Arg	Gly	Ser	Gly	Glu	Gly	Gly	Pro	Gln	Gly	Asn	Ser
			180					185					190		
Ser	Ala	Gly	Trp	Ala	Val	Ala	Ser	Pro	Cys	۸la	Ile	Ala	Asn	Met	Asp
		195					200					205		_	
Phe	Val	Met	۸la	Leu	Ile	Tyr	Val	Met	Leu	Leu	Leu	Leu	Gly	Ala	Phe
	210					215					220				
Leu	Gly	Ala	Trp	Pro	Ala	Leu	Cys	Gly	Arg	Tyr	Lys	Arg	Trp	Arg	Lys
225					230			•		235	٠			,	240
His	Gly	Val	Phe	Val	Leu	Leu	Thr	Thr	Ala	Thr	Ser	Val	Ala	Ile	Trp
				245					250					255	
Val	Val	Trp	Ile	Val	Met	Tyr	Thr	Tyr	Gly	Asn	Lys	Gln	His	Asn	Ser
			260					265						:	,
Pro	Thr	Trp	Asp	Asp	Pro	Thr	Leu	Ala	lle	Ala	Leu	Ala	Ala	۸sn	Ala
		275					280					285			٠.
															Thr
	·290	. : :	٠.٠.	-		295	. • •				300	4		•	;
Lvs	Ser	Ser	Pro	Glu	Gln	Ser	Tvr	Gln	Glv	Asn	Met	Tur	Pro	Thr	Ara

305				•	310					315			•		320	
Gly	Val	Gly	Tyr	Glu	Thr	Ile	Leu	Lys	Glu	Gln	Lys	Gly	Gln	Ser	Met	
	:	;		325					330		,		. • .	335	.*.	
Phe	Val	Glu	Asn	Lys	Ala	Phe	Ser	Met	Asp	Glu	Pro	Val	Ala	Ala	Lys	
	:.		340		: •			345		•			350		٠.	
Arg	Pro	Val	Ser	Pro	Tyr	Ser	Gly	Tyr	Asn	G1 y	Gln	Leu	Leu	Thr	Ser	
		355					360					365				
Val	Tyr	Gln	Pro	Thr	Glu	Met	Ala	Leu	Met	His	Lys	Val	Pro	Ser	Glu	
	370		• •			375					380					
Gly	Ala	Tyr	Asp	Ile	Ile	Leu	Pro	Arg	Ala	Thr	Ala	Asn	Ser	Gln	Val	
385	٠.	-		·	390					395					400	
Met	Gly	Ser	Ala	Asn	Ser	Thr	Leu	Arg	Ala	Glu	Asp	Met	Tyr	Ser	Ala	
	٠.			405					410					415		
Gln	Ser	His	Gln	Ala	Ala	Thr	Pro	Pro	Lys	Asp	Gly	Lys	Asn	Ser	Gln	
	. ;	٠	420					425					430		. • .	
Val	Phe	Arg	Asn	Pro	Tyr	Val	Trp	Λsp			-					
	1+1	435				•	440							•	• •	
							,									
<21	0> 9	6			٠			* *		. ,	•			, .	`,	1 -
<21	1> 2	65	٠.													
<21	2> · P	RT .					•				٠		. ,		. 1	
<21	3> H	lomo	sapi	ens										٠.,		
<40	0> 9	6		••			, •	•		٠	· ;	. :	•	•	11.5	•
Met	Ala	Ala	Ala	Val	Pro	Lys	Arg	Met	Arg	Gly	Pro	Ala	Gln	Ala	Lys	
,	23.	;		· •		, ,	,	,	10	, , ;	•	. :		15		

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Leu	Leu	Pro	Gly	Ser	Ala	Ile	Gln	Ala	Leu	Val	Gly	Leu	Ala	Arg	Pro	
	•		20				•	25					30			
Leu	Val	Leu	Ala	Leu	Leu	Leu	Val	Ser	Ala	Ala	Leu	Ser	Ser	Val	Val	
	٠.	35					40					45				
Ser	Arg	Thr	Asp	Ser	Pro	Ser	Pro	Thr	Val	Leu	Asn	Ser	His	Ile	Ser	
	50					55					60					
Thr	Pro	Asn	Val	Asn	Ala	Leu	Thr	His	Glu	Asn	Gln	Thr	Lys	Pro	Ser	
65					70					75					80	
Ile	Ser	Gln	Ile	Ser	Thr	Thr	Leu	Pro	Pro	Thr	Thr	Ser	Thr	Lys	Lys	
				85					90					95		
Ser	Gly	Gly	Λla	Ser	Val	Val	Pro	His	Pro	Ser	Pro	Thr	Pro	Leu	Ser	
			100					105					110			
Gln	Glu	Glu	Ala	Asp	Asn	Asn	Glu	Asp	Pro	Ser	Ile	Glu	Glu	Glu	Asp	
		115					120					125				
Leu	Leu	Met	Leu	Asn	Ser	Ser	Pro	Ser	Thr	Λla	Lys	Asp	Thr	Leu	Asp	
	130					135					140		:		. :	
Asn	Gly	Asp	Tyr	Gly	Glu	Pro	Asp	Tyr	Asp	Trp	Thr	Thr	Gly	Pro	Arg	
145					150					155					160	
Asp	Asp	Asp	Glu	Ser	Asp	Asp	Thr	Leu	Glu	Glu	Asn	Arg	Gly	Tyr	Met	
				165					170				•	175	•	
Glu	Ile	Glu	Gln	Ser	Val	Lys	Ser	Phe	Lys	Met	Pro	Ser	Ser	Asn	Ile	
	. ; •	i	180					185					190	, ,		,
Glu	Glu	Glu	Asp	Ser	His	Phe	Phe	Phe	llis	Leu	Ile	lle	Phe	Ala	Phe	
	ŧ. ·	195	. • •				200			,		205		. :	٠.	
Cys	Пе	Ala	Val	Val	Tyr	Ile	Thr	Tyr	His	Asn	Lys	Arg	Lys	lle	Phe	

210		215		220		December 1
Leu Leu Val Gln	Ser Arg	Lys Trp	Arg Asp	Gly Leu	Cys Ser	Lys Thr
225	230	• •	•	235 ·		240
Val Glu Tyr His	Arg Leu	Asp Gln	Asn Val	Asn Glu	Ala Met	Pro Ser
	245		250	• • •	et en mit	255
Leu Lys Ile Thr	Asn Asp					• •
260			265			
-						
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<211> 208						
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<213> Homo sapi	ens	·				
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Met Leu Gly Leu	Leu Val	Ala Leu				
1	5		10)		15
Ala Leu Leu Asp						
20			25	•	30)
Arg Ala Arg Leu	Leu Gln	Pro Arg				
35		40		•	45	• • • • • • • • • • • • • • • • • • • •
Arg Phe Pro Gly						
50	. ' '	55	•	60)	· · · · · · · · · · · · · · · · · · ·
Met Asn Asn Ala						
65						
His Leu Thr Arg						
Section of the	85		. ı 9() : - : - : - : - : - : - : - : - : - :	$(-1, \cdots, n)$	95

Company of the property

His	Thr	Val	Leu	Ala	Ala	Ser	Cys	Ala	Arg	His	Arg	Arg	Ser	Lei	ı Arg	
	٠.		100					105		٠.			110)		
Leu	Leu	Glu	Pro	Phe	Glu	Val	Arg	Thr	Arg	Leu	Leu	Gly	Trp	Asp	Asp	٠
		115					120)				125				
Arg	Ala	Phe	Tyr	Leu	Glu	Ala	Arg	Phe	Val	Ser	Leu	Arg	Λsp	Gly	Phe	
	130					135					140					
Val	Cys	Ala	Leu	Leu	Arg	Phe	Arg	Gln	His	Leu	Leu	Gly	Thr	Ser	Pro	
145					150					155					160	
Glu	Λrg	Val	Val	Gln	His	Leu	Cys	Gln	Arg	Arg	Val	Glu	Pro	Pro	Glu	
				165					170					175		
Leu	Pro	Ala	Asp	Leu	Gln	His	Trp	lle	Ser	Tyr	Asn	Glu	Ala	Ser	Ser	
			180					185					190			
Gln	Leu	Leu	Arg	Met	Glu	Ser	Gly	Leu	Ser	Asp	Val	Thr		Asp	Gln	
		195					200			•		205	•	•		
<210	>98	.														
<211	•	•			•	•					•	, .		•. •		
<212																
<213	> Ho	mo s	apie	ns												
															•	
								Ser								•
															().	•
								Leu								
ug /	JIG .	ren (υIU	ırp	rne .	ser	Ala	val	٧ai	Asn	He	Glu	lyr	٧al	Asp	

Į₃ ↔	[:] 35		٠,	٠.	i	40					45			·	٠.
Pro Gln	Thr	Asn	Leu	Thr	Val	Trp	Ser	Val	Ser	Glu	Ser	Gly	Arg	Phe	
50	•	'	٠.		55				'	60		•			
Gly Asp	Ser	Ser	Pro	Lys	G1u	Gly	Ala	His	Gly	Leu	Val	Gly	Val	Pro	
65			. •	70		. *			75				•	80	•
Trp Ala	Pro	Gly	Gly	Asp	Leu	Glu	Gly	Cys	Ala	Pro	Asp	Thr	Arg	Phe	
			85					90	•			٠	95	•. **	
Phe Val	Pro	Glu	Pro	Gly	Gly	Arg	Gly	Ala	Ala	Pro	Trp	Val	Ala	Leu	
		100	,				105			ur i		110	:		
Val Ala	Arg	Gly	Gly	Cys	Thr	Phe	Lys	Asp	Lys	Val	Leu	Val	Ala	Ala	
	115	•				120			•		125				
Arg Arg	Asn	Λla	Ser	Ala	Val	Val	Leu	Tyr	Asn	Glu	Glu	Arg	Tyr	Gly	
130					135					140			•		•
Asn Ile	Thr	Leu	Pro	Met	Ser	His	Ala	Gly	Thr	Gly	Asn	Ile	Val	Val	
145				150					155					160	
Ile Met	Ile	Ser	Tyr	Pro	Lys	Gly	Arg	Glu	Ile	Leu	Glu	Leu	Val	Gln	
			165					170					175	•	
Lys Gly	Ile	Pro	Val	Thr	Met	Thr	Ile	Gly	Val	Gly	Thr	Arg	His	Val	
		180					185			•	•	190	•	•	•
Gln Glu	Phe	lle	Ser	Gly	Gln	Ser	Val	Val	Phe	Val	Λla	lle	Ala	Phe	•
	195	¢				·200			•		205		-	· T	•
Ile Thr	Met	Met	lle	Ile	Ser	Leu	Ala	Trp	Leu	Ile	Phe	Tyr	Tyr	Ile	
210	· ·			,	215				• •,	220	:		. **	'.	•
Gln Arg	Phe	Leu	Tyr	Thr	Gly	Ser	Gln	Ile	Gly	Ser	Gln	Ser	His	Arg	
225		ι		· 230			٠.		235	٠.	, ,	• •••	ورقها	240	٠.,

Lys	Glu	Thr	Lys	Lys	Val	Ile	Gly	Gln	Leu	Leu	Leu	His	Thr	Val	Lys
	· •, ·			245	. •	٠.			250					255	
His	Gly	Gļu	Lys	Gly	Ile	Лsp	Val	Asp	Ala	Glu	Asn	Cys	Ala	Val	Cys
		٠.	260				-	265					270		: •
Ιle	Glu	Asn	Phe	Lys	Val	Lys	Asp	Ile	Ile	Arg	Ile	Leu	Pro	Cys	Lys
	٠.	275					280					285			
His	Ile	Phe	His	Arg	Ile	Cys	Ile	Asp	Pro	Trp	Leu	Leu	Asp	llis	Arg
	290				-	295					300				
Thr	Cys	Pro	Met	Cys	Lys	Leu	Asp	Val	Ile	Lys	Ala	Leu	Gly	Tyr	Trp
305					310					315					320
Gly	Glu	Pro	Gly _,	Asp	Val	Gln	Glu	Met	Pro	Ala	Pro	Glu	Ser	Pro	Pro .
				325					330					335	
Gly	Arg	Asp	Pro	Ala	Ala	Asn	Leu	Ser	Leu	Λla	Leu	Pro	Asp	Asp	Asp
			340					345					350		
Gly	Ser	Asp	Glu	Ser	Ser	Pro	Pro	Ser	Ala	Ser	Pro	Λla	Glu	Ser	Glu
		355	. •		٠.		360					365			
Pro	Gln	Cys	Asp	Pro	Ser	Phe	Lys	Gly	Λsp	Ala	Gly	Glu	Asn	Thr	Λla
	370					37 5					380				
Leu	Leu	Glu	Ala	G1 y	Arg	Ser	Asp	Ser	Arg	His	Gly	Gly	Pro	Ile	Ser
385					390				•	395			•:		400
	<i>t</i> :										,				
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<212	?;.PF	RT ₅ .	: •	,					ī	٠.	•				·. i
<213	3> Hc	omo s	apie	ns									:		

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<400)>. 99	9 ′	. :	•	•	•••			•	•		٠	* . •			•
Met	Phe	Cys	Pro	Leu	Lys	Leu	He	Leu	Leu	Pro	Val	Leu	Leu	Asp	Tyr	
1	., .,	•		´ 5	•		·		10			٠		15		
Ser	Leu	Gly	Leu	Asn	Asp	Leu	Asn	Val	Ser	Pro	Pro	Glu	Leu ·	Thr	Val	
		٠٠,	20	. •	٠,	•	• •	25		٠		•	30		•	-
His	Val	Gly	Asp	Ser	Ala	Leu	Met	Gly	Cys	Val	Phe	Gln	Ser	Thr	Glu	
		35					40					45				
Λsp	Lys	Cys	He	Phe	Lys	Ile	Asp	Trp	Thr	Leu	Ser	Pro	G1 y	Glu	His	
	· 50	٠.	. •			· 55					60		•			
Ala	Lys	Λsp	Glu	Tyr	Val	Leu	Tyr	Tyr	Tyr	Ser	Asn	Leu	Ser	Val	Pro	
65					70		٠			75			•		80	
Ile	Gly	Arg	Phe	Gln	Asn	Arg	Val	His	Leu	Met	Gly	Asp	Asn	Leu	Cys	
				85					90					95		
Asn	Asp	Gly	Ser	Leu	Leu	Leu	G1n	Asp	Val	Gln	Glu	Ala	Asp	Gln	Gly	
	• • •		100				•	105	٠				110	•	٠.	
Thr	Tyr	lle	Cys	Glu	Ile	Arg	Leu	Lys	Gly	Glu	Ser	Gln	Val	Phe	Lys	
		115			•		120					125		. •	+	
Lys	Ala	Val	Val	Leu	His	Val	Leu	Pro	Glu	Glu	Pro	Lys	Glu	Leu	Met	
	130			•		135					140	٠.				•
Val	His	Val	Gly	Gly	Leu	Ile	Gln	Met	Gly	Cys	Val	Phe	Gln	Ser	Thr	
145				٠	150					155					160	
Glu	Val	Lys	His	Val	Thr	Lys	Val	Glu	Trp	lle	Phe	Ser	Gly	Arg	Arg	
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gtc	ggc	cct	ttc	cca	gga	ctg	aac	atg	aag	agt	tat	gcc	ggc	ttc	ctc	•	301
Val	Gly	Pro	Phe	Pro	Gly	Leu	Asn	Met	Lys	Ser	Tyr	Ala	Gly	Phe	Leu		
	: ,	· 65		٠,	•	,	70	•	1.		. :	75	, 1	•	•. •	. •	
acc	gtg	aat	aag	act	tac	aac	agc	aac	ctc	ttc	ttc	tgg	ttc	ttc	cca		349
Thr	Val	Asn	Lys	Thr	Tyr	Asn	Ser	Λsn	Leu	Phe	Phe	Trp	Phe	Phe	Pro	٠.	
	80					85					90				-		
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Ala	Gln	Ile	Gln	Pro	Glu	Asp	Ala	Pro	Val	Val	Leu	Trp	Leu	Gln	Gly		
95					100					105					110		
ggg	ccg	gga	ggt	tca	tcc	atg	ttt	gga	ctc	ttt	gtg	gaa	cat	ggg	cct		445
Gly	Pro	Gly	Gly	Ser	Ser	Met	Phe	Gly	Leu	Phe	Val	Glu	llis	Gly	Pro		
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tat	gtt	gtc	aca	agt	aac	atg	acc	ttg	cgt	gac	aga	gac	ttc	ccc	tgg	•	493
Tyr	Val	Val	Thr	Ser	Asn	Met	Thr	Leu	Arg	Asp	Arg	Asp	Phe	Pro	Trp	•	
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Thr	Thr	Thr	Leu	Ser	Met	Leu	Tyr	Ile	Asp	Asn	Pro	Val	Gly	Thr	Gly		
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ttc	agt	ttt	act	gat	gat	acc	cac	gga	tat	gca	gtc	aat	gag	gac	gat		589
Phe															Asp		
	160	•	•		,	165		,	•		170	, .:	:.	1	3		
gta	gca	cˈgg	gat	tta	tac	agt	gca	cta	att	cag	ttt	Ltc	cag	ata	ttt		637
Val	Ala	Ara	Asn	Leu	Tvr	Ser	Ala	Leu	Ile	Gln	Pho	Phe	Gln	Ile	Phe	.:	

175	5				180)				185	5				190		
cct	gaa	a ta	t aaa	a aa t	. aat	gad	: ttt	tat	gto	act	ggs	g gag	tc1	t tai	t gca		685
Pro	Glu	ту:	r Lys	s Asr	Asn	Asp	Phe	yr Tyr	· Val	Thr	Gly	/ Glu	ı Ser	Туг	Ala		
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Gly	Lys	Туг	- Val	Pro	Ala	Ile	Ala	His	Leu	Ile	His	Ser	Leu	Asn	Pro		
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Val	Arg	Glu	ı Val	Lys	Ile	Asn	Leu	Asn	Gly	lle	Ala	Ile	Gly	Asp	Gly		
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Tyr	Ser	Asp	Pro	Glu	Ser	Ile	Ile	Gly	Gly	Tyr	Ala	Glu	Phe	Leu	Tyr		
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Gln	He	Gly	Leu	Leu	Asp	Glu	Lys	Gln	Lys	Lys	Tyr	Phe	Gln	Lys	G1n		
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Cys	His	Glu	Cys	Ile	Glu	His	lle	Arg	Lys	Gln	Asn	Trp	Phe	Glu	Ala		
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Phe	G1ų	Ile	Leu	Asp	Lys	Leu	Leu	Asp	Gly	Asp	Leu	Thr	Ser	Asp	Pro		
	····	11	290	-				295		٠.			300				
tct	ţac,	ttc	cag	aat	gtt	aca	gga	tgt	agt	aat	tac	tat	aac	ttt	ttg		1021
Ser	Tyr	Phe	Gln	Asn	Val	Thr	G1 y	Cys	Ser	۸sn	Tyr	Tyr	Asn	Phe	Leu		
	1.13	305	2.4	; •	; .	1	310	٠,.	٠٠.	ا مار	٠,,٠	315	:		* a!! .	_	

cgg	tgc	acg	gaa	cct	gag	gat	cag	ctt	tac	tat	gtg	aaa	ttt	ttg	tca	1069
Arg	Cys	Thr	G1ų	Pro	Glu	Asp	Gln	Leu	Tyr _.	Tyr	Val	Lys	Phe	Leu	Ser	•
	320	٠.		;		325			٠.		330	: .		٠.	•	
ctc	cca	gag	gtg	aga	caa	gcc	atc	cac	gtg	ggg	aat	cag	act	ttt	aat	1117
Leu	Pro	Glu	Val	Arg	Gln	Ala	Ile	His	Val	Gly	Asn	Gln	Thr	Phe	Asn 🕆	
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Val	Lys	Pro	Trp	Leu	Thr	Glu	Ile	Met	Asn	Asn	Tyr	Lys	Val	Leu	Ile	٠
	٠٠,		370					375					380			
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Tyr	Asn	Gly	Gln	Leu	Asp	Ile	Ile	Val	Ala	Ala	Ala	Leu	Thr	Glu	His	
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Ser	Leu	Met	Gly	Met	Asp	Trp	Lys	Gly	Ser	Gln	Glu	Tyr	Lys	Lys	Λla	•
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Glu	Lys	Lys	: Val	Trp	Lys	Ile	Phe	Lys	Ser	Asp	Ser	Glu	Val	Ala	Gly	
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Tyr	Ile	Arg	Gln	Ala	Gly	Asp	Phe	His	Gln	Val	Ile	lle	Arg	Gly	Gly	
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Asn Arg Phe Ile Tyr Gly Lys Gly Trp Asp Pro Tyr Val Gly	
465 470 475	
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Met Ser Arg Ala Gln Ile Trp Ala Leu Val Ser Gly Val	
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gga ggg ttt gga gct ctc gtt gct gct acc acg tcc aat gag tgg aaa	278
Gly Gly Phe Gly Ala Leu Val Ala Ala Thr Thr Scr Asn Glu Trp Lys	

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gtg	acc	acg	cga	gcc	tcc	tcg	gtg	ata	aca	gcc	ạct	tgg	gtt	tac	cag		326
Val	Thr	Thr	Arg	Ala	Ser	Ser	Val	Ilė	Thr	Ala	Thr	Trp	Val	Tyr	Gln		
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Gly	Leu	Trp	Met	Asn	Cys	Ala	Gly	۸sn	Ala	Leu	Gly	Ser	Phe	His	Cys	•	
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Phe	Ala	Leu	Phe	Gly	Met	Lys	Cys	Thr	Lys	Val	Gly	Gly	Ser	Asp	Lys		
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Ala	Lys	Ala	Lys	Ile	Ala	Cys	Leu	Ala	Gly	Ile	Val	Phe	Ile	Leu	Ser		
110		•			115		•	•	٠	120			• •	•	125		
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Gly	L'eu	Cys	Ser	Met	Thr	Gly	Cys	Ser	Leu	Tyr	Ala	Asn	Lys		Thr		
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		•			cct												662
Thr	Glu	Phe	Phe	Aśp					Glu						Gly '		
	•	-	145	• •			٠.	150	•		-	** *	155	• • • •	+ 1 · 2		

gcc gct ctg ttt att gga tgg gca gga gcc tca ctg tgc ata att ggt	710
Ala Ala Leu Phe Ile Gly Trp Ala Gly Ala Ser Leu Cys Ile Ile Gly	
160 165 170	
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Gly Val Ile Phe Cys Phe Ser Ile Ser Asp Asn Asn Lys Thr Pro Arg	
175 180 185	
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Tyr Thr Tyr Asn Gly Ala Thr Ser Val Met Ser Ser Arg Thr Lys Tyr	
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His Gly Gly Glu Asp Phe Lys Thr Thr Asn Pro Ser Lys Gln Phe Asp	
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Val Leu Leu Ala Ser Leu Gly Val Gly Leu Val Thr Leu Leu Gly Leu	
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gct gtg ggc tcc tac ttg gtt cgg agg tcc cgc cgg cct cag gtc act) :
Ala Val Gly Ser Tyr Leu Val Arg Arg Ser Arg Arg Pro Gln Val Thr	
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Leu Leu Asp Pro Asn Glu Lys Tyr Leu Leu Arg Leu Leu Asp Lys Thr	
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Thr Val Ser His Asn Thr Lys Arg Phe Arg Phe Ala Leu Pro Thr Ala	
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His His Thr Leu Gly Leu Pro Val Gly Lys His Ile Tyr Leu Ser Thr	
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cga att gat ggc agc ctg gtc atc agg cca tac act ect gtc acc agt 342	?
Arg Ile Asp Gly Ser Leu Val Ile Arg Pro Tyr Thr Pro Val Thr Ser	
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gat gag gat caa ggc tat gtg gat ctt gtc atc aag gtc tac ctg aag 390)

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Gly	Val	His	Pro	Lys	Phe	Pro	Glu	Gly	Gly	Lys	Met	Ser	Gln	Tyr	Leu	
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Gly	Gly	Thr	Gly	Ile	Thr	Pro	Met	Leu	Gln	Leu	Ile	Arg	Ala	lle	Leu	
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Thr	Glu	Lys	Asp	, [le	Ile	Leu	Arg	,Glu,	Asp	Leu	Glu	Glu	Leu	Ģ1n	Ala	
	. • •	٠,	ŧ.	220	: -		. 1		225	••	:	. •		230		
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Glu His Leu	Pro Ala Pro	Gly Asp Asp	Val Leu Va	l Leu Leu Cys	Gly
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ggc tac tca	caa aag atg	cga ttc acc	tac tg agc	atcctcc agctt	ccctg 970
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AND SHEET OF THE FORMER

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Arg	Leu	Val	Thr	Ala	Ala	Leu	Leu	Leu	Gly	Leu	Met	Met	Val	Val	Thr			
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Gly	Asp,	Glu	Asp	Glu	Asn	Ser	Pro	Cys	Ala	His	Glju	Ala	Leu	Leu	Asp			
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Glu	Asp	Thr	Leu	Phe	Cys	Gln	Gly	Leu	Glu	Val	Phe	Tyr	Pro	Glu	Leu			
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Ile	Lys	Gly	Ala	Asp	Leu	Lys	Lys	Gly	Lys	Ile	Gln	Gly	Gln	Glu	Leu		
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Ser	Ala	Tyr	Gln	Ala	Pro	Ser	Pro	Pro	Ala	His	Ser	Gly	Phe	His	Arg		
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tac	cag	ttc	ttt	gtc	tat	ctt	cag	gaa	gga	aaa	gtc	atc	tct	ctc	ctt		593
Tyr	Gln	Phe	Phe	Val	Tyr	Leu	Gln	Glu	Gly	Lys	Val	Ile	Ser	Leu	Leu		
150	<i>i.</i>	1.	٠.		155	• •		•	•.	160		. ••	٠.	,	165	;	
ccc	aag	gaa	aac	aaa	act	cga	ggc	tct	tgg	aaa	atg	gac	aga	ttt	ctg		641
Pro	Lys	Glu	Asn	Lys	Thr	Arg	Gly	Ser	Trp	Lys	Meț	Asp	Arg	Phe	Leu		
	,;		٠	170	1		٠.	•	175	•	•		٠	180	ζ, .	•	
aac	cgt	ttc	cac	ctg	ggc	gaa	cct	gaa	gca	agc	acc	cag	ttc	atg	acc		689
Asn	Arg	Phe	His	Leu	Gly	Glu	Pro	Glu	Ala	Ser	Thr	Gln	Phe	Met	Thr		
	4. 1		185	•		٠٠.	٠	190	٠		٠	•	195	٠.	٠.		
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Gln	Asn	Tyr	Gln	Asp	Ser	Pro	Thr	Leu	Gln	Ala	Pro	Arg	Glu	Arg	Ala	٠,	

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agc gag ccc aag cac aaa aac	cag gcg gag ata gct	gcc tgc t. 780
Ser Glu Pro Lys His Lys Asn	Gln Ala Glu Ile Ala	Ala Cys
215 220	. 225	÷
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gagcciggcc igggagccag g aig	gcc atc cac aaa gcc	ttg gtg atg tgc 171
Met	Ala Ile His Lys Ala	Leu Val Met Cys
$(s_{ij} \circ f) \cong (s_{ij} \circ g) \circ (1)$	5	. 10
ctg gga ctg cct ctc ttc ctg	ttc cca ggg gcc tgg	gcc cag ggc cat 219
Leu Gly Leu Pro Leu Phe Leu	Phe Pro Gly Ala Trp	Ala Gln Gly His
.15	· 20	25
gte eca ece gge tge age caa	ggc ctc aac ccc ctg	tac tac aac ctg 267
Val Pro Pro Gly Cys Ser Gln	Gly Leu Asn Pro Leu	Tyr Tyr Asn Leu 🛒

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Cys	Asp	Arg	Ser	Gly	Ala	Trp	Gly	Ile	Val	Leu	Glu	Ala	Val	Ala	Gly		
		45			٠		50					55			*- • •		
gcg	ggc	att	gtc	acc	acg	ttt	gtg	ctc	acc	atc	atc	ctg	gtg	gcc	agc	•	363
Ala	Gly	Ile	Val	Thr	Thr	Phe	Val	Leu	Thr	Ile	Ile	Leu	Val	Ala	Ser		
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Leu	Pro	Phe	Val	Gln	Asp	Thr	Lys	Lys	۸rg	Ser	Leu	Leu	Gly	Thr	Gln	1	
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Val	Phe	Phe	Leu	Leu	Gly	Thr	Leu	Gly	Leu	Phe	Cys	Leu	Val	Phe	Ala		
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Cys	Val	Val	l.ys	Pro	Asp	Phe	Ser	Thr	Cys	Ala	Ser	Arg	Arg	Phe	Leu	•	
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Phe	Gly	Val	Leu	Phe	Ala	Ile	Cys	Phe	Ser	Cys	Leu	Ala	Ala	His	Val		
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Phe															Trp		
															و نداد		65.1
															atc		651
Val	He	Phe	Thr	· Val	. Ala	Leu	Leu	ı Leu	Thr						lle		
					100		_			169			- · ·		. 170		

A CONTRACT OF THE STORY

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gcc	atc	gcc	aac	atg	gac	ttt	gtc	atg	gca	ctc	atc	tac	gto	atg	ctg	795
Ala	Ile	Ala	Asn	Met	Asp	Phe	Val	Met	Ala	Leu	Ile	Tyr	Val	Met	Leu	
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Thr	Ser	Val	Ala	He	Trp	Val	Val	Trp	Ile	Val	Met	Tyr	Thr	Tyr	Gly	
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Asn	Lys	Gln	His	Asn	Ser	Pro	Thr	Trp	Asp	Asp	Pro	Thr	Leu	Ala	Ile	
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Ala	Leu	Ala	Ala	Λsn	Ala	Trp	Ala	Phe	Val	Leu	Phe	Tyr	Val	Ile	Pro	
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His	Lys	Val	Pro	Ser	Glu	Gly	Ala	Tyr	Asp	Ile	Ile	Leu	Pro	Arg	Ala		
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Thr	Ala	Asn	Ser	Gln	Val	Met	Gly	Ser	Ala	Asn	Ser	Thr	Leu	Arg	Ala	٠	
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gaa	gac	atg	tac	tcg	gcc	cag	agc	cac	cag	gcg	gcc	aca	ccg	ccg	aaa		1419
Glu	Asp	Met	Tyr	Ser	Ala	Gln	Ser	His	Gln	Ala	Ala	Thr	Pro	Prò	Lys	•	
	٠.	٠.,		415		:		.:	420		•		1.5	425	. ** *		
gac	ggc	aag	aac	tct	cag	gtc	ttt	aga	aac	ccc	tac	gtg	tgg	gac			1464
Asp	Gly	Lys	Asn	Ser	Gln	Val	Phe	Λrg	Asn	Pro	Tyr	Väl	Trp	Asp	+:24		

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gct gcc gtc ccg aag agg atg agg	ggg cca gca	caa gcg aaa ctg ctg	103
Ala Ala Val Pro Lys Arg Met Arg	Gly Pro Ala	Gln Ala Lys Leu Leu	
5 3 5 y 10	• • • • • • • • • • • • • • • • • • •	. 15 ₇	
ccc ggg tcg gcc atc caa gcc ctt	gtg ggg ttg	gcg cgg ccg ctg.gtc	151
Pro Gly Ser Ala Ile Gln Ala Leu	Val Gly Leu	Ala Arg Pro Leu Val	

RNSDOCID - WO ... DII SEEDAS I -

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Leu	Ala	Leu	Leu	Leu	Val	Ser	Ala	Ala	Leu	Ser	Ser	Val	Val	Ser	Arg		
35		٠.		·	40	•				45	, .	•4	.:		50	٠.,	
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Thr	Asp	Ser	Pro	Ser	Pro	Thr	Val	Leu	Asn	Ser	His	Ile	Ser	Thr	Pro		
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Asn	Val	Asn	Ala	Leu	Thr	His	Glu	Asn	Gln	Thr	Lys	Pro	Ser	He	Ser		
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Gln	Ile	Ser	Thr	Thr	Leu	Pro	Pro	Thr	Thr	Ser	Thr	Lys	Lys	Ser	Gly		
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Gly	Ala	Ser	Val	Val	Pro	His	Pro	Ser	Pro	Thr	Pro	Leu	Ser	Gln	Glu		
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gaa	gct	gat	aac	aat	gaa	gat	cct	agt	ata	gag	gag	gag	gat	ctt	ctc	,	439
G]u	Ala	Asp	Asn	Asn	Glu	Asp	Pro	Ser	He	Glu	Glu	Glu	Asp	Leu	Ĺeu		
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Asp	Tyr	Gly	Glu	Pro	Asp	Tyr	Asp	Trp	Thr	Thr	Gly	Pro	Arg	Asp	Asp'	٠.	
	1		150	٠, .				155		, .		;	160	و ن	740	1	

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Glu	Gln	Ser	Val	Lys	Ser	Phe	Lys	Met	Pro	Ser	Ser	Asn	Ile	Glu	Glu	
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Glu	Asp	Ser	llis	Phe	Phe	Phe	His	Leu	Ile	Ile	Phe	Ala	Phe	Cys	Ile	
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Ala	Val	Val	Tyr	He	Thr	Tyr	His	Asn	Lys	Arg	Lys	Tle	Phe	Leu	Leu	
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Tyr	His	Arg	Leu	Asp	Gln	Asn	Val	Asn	Glu	Ala	Met	Pro	Ser	Leu	Lys	
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att	acc	aat	gat	tat	att	ttt	taaa	agc a	actg	tgati	tt ga	att	tgct	t		870
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ENSULUTION - MUSEUMS I -

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⟨211⟩ 2180

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		Ме	t Le	u Gl	y Le	u Le	u Va	1 A1	a Le	u Le	u Al	a Le	eu Gl	y Le	u Al	a	
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gtc	ttt	gcg	ctg	ctg	gac	gtc	tgg	tac	ctg	gtg	cgc	ctt	ccg	tgc	gcc		158
Val	Phe	Ala	Leu	Leu	Asp	Val	Trp	Tyr	Leu	Val	Arg	Leu	Pro	Cys	Ala		
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gtg	ctg	cgc	gcg	cgc	ctg	ctg	cag	ccg	cgc	gtc	cgt	gac	ctg	cta	gct		206
Val	Leu	Arg	Ala	Arg	Leu	Leu	Gln	Pro	Arg	Val	Arg	Asp	Leu	Leu	Ala		
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Glu	Gln	Arg	Phe	Pro	Gly	Arg	Val	Leu	Pro	Ser	Asp	Leu	Asp	Leu	Leu	:	
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Leu	His	Met	Asn	Asn	Ala	Arg	Tyr	Leu	Arg	Glu	Ala	Asp	Phe	Ala	Arg		
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Val	Ala	His	Leu	Thr	Arg	Cys	Gly	Val	Leu	Gly	Λla	Leu	Arg	Glu	Leu		
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Arg	Ala	llis	Thr	Val	Leu	Ala	Ala	Ser	Cys	Ala	Arg	His	Arg	Arg	Ser	100	
95	• • •	٠.	٠,	,	100	• •			٠.	1.05	٠	• • •		. ,	110	. •	

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	·		•					, ,			ŀ	det /	Ala ´	Trp /	Arg	•		
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cgg	ċgc	gaa	gcc	agc	gtc	ggg	gct	cgc	ggc	gtg	ttg	gct	ctg	gcg	ttg		162	
Arg	Arg	Glu	Ala	Ser	Val	Gly	Ala	Arg	Gly	Val	l.eu	Ala	Leu	Λla	Leu			
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lle	Ile	Ser	Leu	Ala	Trp	Leu	Ile	Phe	Tyr	Tyr	Ile	Gln	Arg	Phe	Leu	
	٠	215	*				220	. •	:	. •		225		* *		
tai	act	ggc	tet	กลช	att	gga	aat	cag	200	cat	202	222	gaa	act	аас	834

Tyr	Thr	Gly	Ser	Gln	Ile	Gly	Ser	Gln	Ser	His	Arg	Lys	Glu	Thr	Lys		
	230	.:.			,. •	235	,	٠.	;		240	1	1.1.	.* '	۳		
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Lys	Val	Lys	Asp	Ile	He	Λrg	Ile	Leu	Pro	Cys	Lys	His	Ile	Phe	His		
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Cys	Lys	Leu	Asp	Val	Ile	Lys	Ala	Leu	Gly	Tyr	Trp	Gly	Glu	Pro	Gly	• •	
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Asp	Val	Gln	Glu	Met	Pro	Ala	Pro	Glu	Ser	Pro	Pro	Gly	Arg	Asp	Pro		
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Ala	Ala	Asn	Leu	Ser	Leu	Ala	Leu	Pro	Asp	Asp	Asp	Gly	Ser	Λsp	Glu	. • •	
	٠			345			* 1		350			٠.	٠,	355	. و د	••	
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cage atg ttt tgc cca ctg aaa ctc	atc ctg ctg	cca gtg tta ctg gat	169
Met Phe Cys Pro Leu Lys Leu	Ile ¡Leu Leu	Pro Val Leu Leu Asp	
4-1 63 47 37 4 5 5 4 5 4 5	10		

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Tyr	Ser	Leu	Gly	Leu	Asn	Asp	Leu	Asn	Val	Ser	Pro	Pro	Glu	Leu	Thr	•	
	υ.			20		•	٠.		25		•			30	•		
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Val	His	Val	Gly	Asp	Ser	Ala	Leu	Met	Gly	Cys	Val	Phe	Gln	Ser	Thr		
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His	Ala	Lys	Asp	Glu	Tyr	Val	Leu	Tyr	Tyr	Tyr	Ser	Asn	Leu	Ser	Val		
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Cys	Asn	Asp	Gly	Ser	Leu	Leu	Leu	Gln	Asp	Val	Gln	Glu	Ala	Asp	Gln	٠.	
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Lys	Lys	Ala	Val	Val	Leu	His	Val	Leu	Pro	Glu	Glu	Pro	Lys	Glu	Leu		
	٠	130	1				·135		. 1	, . .		140	· · ·	• . •			
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Thr Glu Val Lys His Val Thr Lys Val Glu Trp Ile Phe Ser Gly Arg	
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Arg Ala Lys Val Thr Arg Arg Lys His His Cys Val Arg Glu Gly Ser	
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Gly Ser Pro Leu Leu Trp Gly Pro Arg Ala Gly Gly Val Gly Leu Leu	i
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Val Leu Leu Leu Gly Leu Phe Arg Pro Pro Pro Ala Leu Cys Ala	
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Glu	Ala	Ala	Gly	Ala	Val	Gln	Glu	Leu	Ala	Arg	Ala	Leu	Ala	His	Leu		
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Leu	Glu	Ala	Glu	Arg	Gln	Glu	Arg	Ala	Arg	Ala	Glu	Ala	Gln	Glu	Ala		
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115	٠, .	·			120					125				. •	130		
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-,-					÷												
cca													gt g	cccc	cgcca	•	880
															N.		
110	260																
															agccag		940
															cagc		
ccc																	
401						,				•	•	, ,			.: .		
			٠					•					• • • •		<i>-</i>		
	1> 3														::		
							·.·		. ,	. '	٠,	1.1	. ; -	10	in Jana 1	•	
<21	3> H	omo	sapi	ens					. ;					· · ·			

, the term of the first term of the first of

<40	0>.1	21						٠	• :	, -					,
Met	Thr	Ala	Gly	Gly	G1n	Ala	Glu	Ala	Glu	Gly	Ąla	Gly	Gly	Glu	Pro
1	:	,		. 5					10			;		15	
Gly	Ala	Ala	Arg	Leu	Pro	Ser	Arg	Val	Ala	Arg	Leu	Leu	Ser	Ala	Leu
			20					25					30		•
Phe	Tyr	Gly	Thr	Cys	Ser	Phe	Leu	Ile	Val	Leu	Val	Asn	Lys	Ala	Leu
		35					40					45			
Leu	Thr	Thr	Tyr	Gly	Phe	Pro	Ser	Pro	Ile	Phe	Leu	Gly	Ile	Gly	Gln
	50					55					60				
Met	Ala	Ala	Thr	Ile	Met	Ile	Leu	Tyr	Val	Ser	Lys	Leu	Asn	Lys	lle
65					70					75					80
Ile	His	Phe	Pro	Asp	Phe	Лsp	Lys	Lys	Ile	Pro	Val	Lys	Leu	Phe	Pro
		•		85					90					95	
Leu	Pro	Leu	Leu	Tyr	Val	Gly	Asn	His	lle	Ser	Gly	Leu	Ser	Ser	Thr
			100					105					110		
Ser	Lys	Leu	Ser	Leu	Pro	Met	Phe	Thr	Val	Leu	Arg	Lys	Phe	Thr	Ile
		115				٠,	120					125			٠, ,٠
Pro	Leu	Thr	Leu	Leu	Leu	Glu	Thr	Ile	Ile	Leu	Gly	Lys	Gln	Tyr	Ser
	130					135			•		140				
Leu	Asn	lle	lle	Leu	Ser	Val	Phe	Ala	Ile	Ile	Leu	Gly	Ala	Phe	Ile
145					150					155					160
Ala	Ala	Gly	Ser	Asp	Leu	Λla	Phe	Asn	Leu	Glu	Gly	Tyr	Ile	Phe -	Va,l
				165					170				!	175	٠.,
Phe	Leu	Asn	Asp	Ile	Phe	Thr	Ala	Ala	Asn	Gly	Val	Tyr	Thr	Lys	Ģln
			180					105					100		

Lys	Met	Asp	Pro	Lys	Glu	Leu	Gly	Lys	Tyr	Gly	Val	Leu	Phe	Tyr	Asn	
	,	195	. • •	. · ·		,	200					205	• •		.··•	
Λla	Cys	Phe	Met	Ile	Ile	Pro	Thr	Leu	lle	Ile	Ser	Val	Ser	Thr	Gly	
	210	,,,,	V 1 4	*. •		215		,	,		220	٠.				
Asp	Leu	Gln	Gln	Ala	Thr	Glu	Phe	Asn	Gln	Trp	Lys	Asn	Val	Val	Phe	
225		٠.			230					235					240	
Ile	Leu	Gln	Phe	Leu	Leu	Ser	Cys	Phe	Leu	Gly	Phe	Leu	Leu	Met	Tyr	
				245			, ,		250	•				255	. •	
Ser	Thr	Val	Leu	Cys	Ser	Tyr	Tyr	Asn	Ser	Ala	Leu	Thr	Thr	Ala	Val	
			260		,			265					270			
Val	Gly	Ala	Ile	Lys	Asn	Val	Ser	Val	Ala	Tyr	Ile	Gly	Ile	Leu	Ile	
	- •	275					280					285		•	11	
Gly	Gly	Asp	Tyr	Ile	Phe	Ser	Leu	Leu	Asn	Phe	Val	Gly	Leu	Asn	Ile	
	290	4.3				295					300	·		٠٠		
Cys	Met	Ala	Gly	Gly	Leu	Arg	Tyr	Ser	Phe	Leu	Thr	Leu	Ser	Ser	Gln	
305	. ·	٠,			310			•		315				٠.	320	
Leu	Lys	Pro	Lys	Pro	Val	Gly	Glu	Glu	Asn	Ile	Cys	Leu	Asp	Leu	Lys	
		1.	. ,	325					330					335	*** I	
Ser											٠				, .;	
	7/-	٠.,				٠	. 1			. •					• • •	
	***										٠					
<21	0> 1	22 '	٠.	٠.	•	. •	* **	• •	•		ı			,	1 .	
	1> 2						٠									
<21	2> P	RT	••	: •	,	.:			. • •		٠.	· • •	• ·	•	;	•
<21	3> H	omo	sapi	ens									** - \$			

in the control of the state at

<40	0> 1	22	:							٠.				٠, ٠	•	
Met	Ala	Glu	Ala	Glu	Glu	Ser	Pro	Gly	Asp	Pro	Gly	Thr	Ala	Ser	Pro	
l	;	. ••		. 5					10	+				15		
Arg	Pro	Leu	Phe	Ala	Gly	Leu	Ser	Asp	Ile	Ser	Ile	Ser	Gln	Asp	Ile	
			20					25					30			
Pro	Val	Glu	Gly	Glu	Ile	Thr	Ile	Pro	Меt	Arg	Ser	Arg	Ile	Arg	Glu	
		35					40					45				
Phe	Asp	Ser	Ser	Thr	Leu	Asn	Glu	Ser	Val	Arg	Asn	Thr	Ile	Met	Arg	
	50					55					60					
Asp	Leu	Lys	Ala	Val	Gly	Lys	Lys	Phe	Меt	His	Val	Leu	Tyr	Pro	Arg	
65					70					75					80	
Lys	Ser	Asn	Thr	Leu	Leu	Arg	Asp	Trp	Asp	Leu	Trp	Gly	Pro	Leu	Ile	
				85					90					95		
Leu	Cys	Val	Thr	Leu	Ala	Leu	Met	Leu	Gln	Arg	Asp	Ser	Ala	Asp	Ser	
			100					105					110			
Glu	Lys	Asp	Gly	Gly	Pro	Gln	Phe	Ala	Glu	Val	Phe	Val	Ile	Val	Trp	
		115					120			. •		125			· ' '	
Phe	Gly	Ala	Val	Thr	lle	Thr	Leu	Asn	Ser	Lys	Leu	Leu	Gly	Gly	Asn	
	130					135					140			•		
lle	Ser	Phe	Phe	Gln	Ser	Leu	Cys	Val	Leu	Gly	Tyr	Cys	Ile	Leu	Pro	
145					150					155			,		160	
Leu	Thr	Val	Ala	Met	Leu	Ile	Cys	Arg	Leu	Val	Leu	Leu	Ala	Asp	Pro	•
	٠,			165			· ·		170	•		. :		175	. •	
Gly	Pro	Val	Asn	Phe	Met	Val	Arg	Leu	Phe	Val	Val	Ile	Val	Met	Phe	
			180			,	. :	185				. ,	190	. •		

Ala Trp Ser Ile Val Ala Ser Thr Ala Phe Leu Ala Asp Ser Gln Pro 195 Pro Asn Arg Arg Ala Leu Ala Val Tyr Pro Val Phe Leu Phe Tyr Phe 210 220 220 220 220 Val Ile Ser Trp Met Ile Leu Thr Phe Thr Pro Gln 235 225 **230** <210> 123 <211> 560 <212> PRT <213> Homo sapiens <400> 123 Met Ala Ala Pro Ala Glu Ser Leu Arg Arg Arg Lys Thr Gly Tyr Ser 10 15 1 5 Asp Pro Glu Pro Glu Ser Pro Pro Ala Pro Gly Arg Gly Pro Ala Gly 20 25 30 Ser Pro Ala His Leu His Thr Gly Thr Phe Trp Leu Thr Arg Ile Val 40 45 Leu Leu Lys Ala Leu Ala Phe Val Tyr Phe Val Ala Phe Leu Val Ala 50 60 60 60 Phe His Gln Asn Lys Gln Leu Ile Gly Asp Arg Gly Leu Leu Pro Cys Arg Val Phe Leu Lys Asn Phe Gln Gln Tyr Phe Gln Asp Arg Thr Scr Trp Glu Val Phe Ser Tyr Met Pro Thr Ile Leu Trp Leu Met Asp Trp

DOCIDI AND DELIBERDA 2 L.S.

	• '.		100					105				-	110		* 1°	
Ser	Asp	Met	Asn	Ser	Asn	Leu	Asp	Leu	Leu	Ala	Leu	Leu	Gly	Leu	Gly	
	. :	115					120			•		125				
Ile	Ser	Ser	Phe	Val	Leu	Ile	Thr	Gly	Cys	Ala	Asn	Met	Leu	Leu	Met	
	130					135					140					
Ala	Ala	Leu	Trp	Gly	Leu	Tyr	Met	Ser	Leu	Val	Asn	Val	Gly	llis	Val	
145					150					155					160	
Trp	Tyr	Ser	Phe	Gly	Trp	Glu	Ser	Gln	Leu	Leu	Glu	Thr	Gly	Phe	Leu	
	,			165					170					175		
Gly	Ile	Phe	Leu	Cys	Pro	Leu	Trp	Thr	Leu	Ser	Arg	Leu	Pro	Gln	His	
			180					185					190			
Thr	Pro	Thr	Ser	Arg	Ile	Val	Leu	Trp	Gly	Phe	Arg	Trp	Leu	Ile	Phe	
		195					200					205				
Arg	lle	Met	Leu	Gly	Ala	Gly	Leu	Ile	Lys	Ile	Arg	Gly	Λsp	Arg	Cys	
	210					215		-			220					
Trp	Arg	Asp	Leu	Thr	Cys	Met	Asp	Phe	His	Tyr	Glu	Thr	Gln	Pro	Met	
225			. •		230		:			235					240	
Pro	Asn	Pro	Val	Ala	Tyr	Tyr	Leu	His	His	Ser	Pro	Trp	Trp	Phe	His	
				245					250					255		
Arg	Phe	Glu	Thr	Leu	Ser	Asn	His	Phe	Ile	Glu	Leu	Leu	Val	Pro	Phe	
	,·		260					265					270			
Phe	Leu	Phe	Leu	Gly	Arg	Arg	Ala	Cys	Ile	Ile	His	Gly	Val	Leu	Gln	
													. •			
Ile	Leu								Ser	Gly	Asn			Phe	Leu	
	290					295					300		•			

Asn	Trp	Leu	Thr	Met	Val	Pro	Ser	Leu	Ala	Cys	Phe	Asp	Asp	Ala	Thr
305	; -	93	,	,	310	٠٠.		;		315		. 1.	• • •	•	320
Leu	Gly	Phe	Leu	Phe	Pro	Ser	Gly	Pro	Gly	Ser	Leu	Lys	Asp	Arg	Val
	. ,	11.1	-	325			•		330	,		٠.		335	٠.
Leu	Gln	Met	Gln	Arg	Asp	lle	Arg	Gly	Ala	۸rg	Pro	Glu	Pro	Arg	Phe
	٠.		340		: .	•		345					350	•	ı
Gly	Ser	Val	Val	Arg	۸rg	Ala	Ala	Asn	Val	Ser	Leu	Gly	Val	Leu	Leu
		355					360					365			•
Ala	Trp	Leu	Ser	Val	Pro	Val	Val	Leu	Asn	Leu	Leu	Ser	Ser	Arg	Gln
	370					375					380				
Val	Met	Asn	Thr	His	Phe	Asn	Ser	Leu	His	Ile	Val	Asn	Thr	Tyr	Gly
385	.* '				390		•	,		395			. •	,	400
Ala	Phe	Gly	Ser	He	Thr	Lys	Glu	Arg	Ala	Glu	Val	Ile	Leu	Gln	Gly
				405					410			•	•	415	
Thr	Ala	Ser	Ser	Asn	Ala	Ser	Ala	Pro	Asp	Ala	Met	Trp	Glu	Asp	Tyr
	.: •		420					425					430	,	•
Glu	Phe	Lys	Cys	Lys	Pro	Gly	Asp	Pro	Ser	Arg	Arg	Pro	Cys	Leu	Ile
		435		;			440					445			
Ser	Pro	Tyr	His	Tyr	Arg	Leu	Asp	Trp	Leu	Met	Trp	Phe	Ala	Ala	Phe
	450				٠.	455		•		••	460				; :
Gln	Thr	Tyr	Glu	His	Asn	Asp	Trp	Ile	Ile	His	Leu	Ala	Gly	Lys	Leu
465		• •			470	•		. •		475		••	•••		480
Leu	Ala	Ser	Asp	Ala	Glu	Ala	Leu	Ser	Leu	Leu	Ala	His	Asn	Pro	Phe
	1	,	•	485	•	•	• • • •	•	490		٠,٠	. ' '	, •	495	, . 1
Ala	Glv	Ara	Pro	Pro	Pro	Arg	Trp	Val	Arg	Gly	Glu	His	Tyr	Arg	Tyr

	1 .		500	٠.		٠		505		•			510		0.0	
Lys	Phe	Ser	Arg	Pro	Gly	Gly	Arg	His	Ala	Λla	Glu	G1 y	Lys	Trp	Trp	
		515			• .		520					525			. •	
Val	Arg	Lys	Arg	Ile	Gly	Ala	Tyr	Phe	Pro	Pro	Leu	Ser	Leu	Glu	Glu	
•	530					535					540					
Leu	Arg	Pro	Tyr	Phe	Arg	Asp	Arg	Gly	Trp	Pro	Leu	Pro	Gly	Pro	Leu	
545					550				•	555					560	
	٠.															
<210	0> 1:	24.														
<21	1> 40	06														
<212	2> PI	RT														
<213	3> H	omo :	sapi	ens												
<400)>- 12	24							٠					,		;
Met	Ala	Glu	Asn	Gly	Lys	Asn	Cys	Asp	Gln	Arg	Arg	Val	Ala	Met	Asn	
1				. 5					10					15		
Lys	Glu	His	His	Asn	Gly	Asn	Phe	Thr	Asp	Pro	Ser	Ser	Val	Asn	Glu	
	٠, -	. • •	20	٠.				25			٠	. •	30		<u>.</u> : '	
Lys	Lys	Arg	Arg	Glu	Arg	Glu	Glu	Arg	Gln	Asn	Ile	Val	Leu	Trp	Arg	
		35					40					45				
Gln	Pro	Leu	Ile	Thr	Leu	Gln	Tyr	Phe	Ser	Leu	Glu	Ile	Leu	Val	Ile	
	50					55				,	60				•.•	
Leu	Lys	Glu	Trp	Thr	Ser	Lys	Leu	Trp	His	Arg	Gln	Ser	Ile	Val	Val	
65	2.60	, ;	-		70				; ;	75				. ,•	80	
Ser	Phe	Leu	Leu	Leu	Leu	Ala	Val	Leu	Ile	Ala	Thr	Tyr	Tyr	Val	Glu	
	me	,	» } ;	85	•	, ; .		11.	90	; •	٠.٠	111 _		, 95		٠,٠

Gly	Val	His	Gln	G1n	Tyr	Val	Gln	Arg	Ile	Glu	Lys	Gln	Phe	Leu	Leu
		. • •	100	,	-			105					110		24.
Tyr	Ala	Tyr	Trp	Ile	Gly	Leu	Gly	Ile	Leu	Ser	Ser	Val	Gly	Leu	Gly
		115	·· -	١			120	,	٠.		,	125	٠.	•	: .
Thr	Gly	Leu	His	Thr	Phe	Leu	Leu	Tyr	Leu	Gly	Pro	His	Ile	Ala	Ser
	130	•			, .	135		••		, -	140			•	. •
Val	Thr	Leu	Λla	Ala	Tyr	Glu	Cys	Asn	Ser	Val	Asn	Phe	Pro	Glu	Pro
145					150					155					160
Pro	Tyr	Pro	Asp	Gln	Ile	Ile	Cys	Pro	Λsp	Glu	Glu	Gly	Thr	Glu	Gly
				165					170					175	,
Thr	Ile	Ser	Leu	Trp	Ser	Ile	Ile	Ser	Lys	Val	Arg	Ile	Glu	Ala	Cys
			180					185					190	٠	
Met	Trp	Gly	Ile	Gly	Thr	Ala	Ile	Gly	Glu	Leu	Pro	Pro	Tyr	Phe	Met
		195					200				•	205			
Ala	Arg	Λla	Λla	Arg	Leu	Ser	Gly	Ala	Glu	Pro	Asp	Asp	Glu	Glu	Tyr
	210					215	•			•	220		٠.		
Gln	Glu	Phe	Glu	Glu	Met	Leu	Glu	His	Ala	Glu	Ser	Ala	Gln	Asp	Phe
225	.* •	-		• • •	230		•			235		٠			240
Ala	Ser	Arg	Ala	Lys	Leu	Ala	Val	Gln	Lys	Leu	Val	Gln	Lys		Gly
		•	•	245	•				250	ı				255	•
Phe	Phe	Gly	Ile	Leu	Ala	Cys	Ala	Ser	Ile	Pro	Asn	Pro	Leu	Phe	Asp
		.:	260		. 9		,	265				•	270	•	1.77
Leu	Ala	Gly	Ile	Thr	Cys	Gly	His	Phe	Leu	Val	Pro	Phe	Trp	Thr	Phe
	د با ما	275		• (•	!	٠,	280		. • •			285	5	٠	: · · · · · ·
Pho	Glv	Ala	Thr	Leu	He	Glv	Lvs	Ala	He	· Ile	Lys	: Met	: His	Ile	Gln

	290		•			295	. •	-			300	٠.	:			
Lys	Ile	Phe	Val	Ιlε	lle	Thr	Phe	Ser	Lys	His	Ile	Val	Glu	G1n	Met	
305		' -			310					315					320	
Val	Ala	Phe	Ile	Gly	Ala	Val	Pro	Gly	Ile	Gly	Pro	Ser	Leu	Gln	Lys	
				325	i				330					335		
Pro	Phe	Gln	Glu	Tyr	Leu	Glu	Ala	Gln	Arg	G1n	Lys	Leu	His	His	Lys	
			340					345					350			
Ser	Glu	Met	Gly	Thr	Pro	G1n	Gly	Glu	Asn	Trp	Leu	Ser	Trp	Met	Phe	
		355					360					365				
Glu	Lys	Leu	Val	Val	Val	Met	Val	Cys	Tyr	Phe	Ile	Leu	Ser	Ile	Ile	
	370					375					380					
Asn	Ser	Met	Ala	Gln	Ser	Tyr	Ala	Lys	Arg	Ile	Gln	Gln	Arg	Leu	Asn	
385					390					395					400	
Ser	Glu	Glu	Lys	Thr	Lys											
				405												
<210	> 12	25 .		•										. ,		
<211	> 45	3														
<212	> PR	T														
<213	> Ho	mo s	apie	ns												
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Met (Gly	Val	Leu	Gly	Arg	Val	Leu	Leu '	Trp	Leu (Gln	Leu 1	Cys	Ala	Leu	
1	٠.			5					10				·	15	- ·.	
Thr (Gln .	Ala	Val	Ser	Lys										Val	
	:		20				•	25	. '		.1	~ 4	30		s i s	٠

Control of the trigger

Ala	Ala	Asn	Trp	Ser	Gln	Asn	Arg	Thr	Pro	Cys	Ala	Gly	Gly	Ala	Val	
	11.	··35	:			• •	40	•	.•	• 1		[:] 45	••	• • .	23	•. '.
Glu	Phe	Pro	Ala	Asp	Lys	Met	Val	Ser	Val	Leu	Val	Gln	Glu	G1y	His	
	- 50	!.	•	.,	•	⁻ 55	١.		•	:	60	. '			1.7	• .
Ala	Val	Ser	Asp	Met	Leu	Leu	Pro	Leu	Asp	Gly	Glu	Leu	Val	Leu	Ala	
65	••	:	,		· 70	٠.		•		75			:		· 80	. 3
Ser	Gly	Ala	Gly	Phe	Gly	Val	Ser	Asp	Val	Gly	Ser	His	Leu	Asp	Cys	
				85		•			90	٠.		٠		95	''	•
Gly	Ala	Gly	Glu	Pro	Ala	Val	Phe	Arg	Asp	Ser	Asp	Arg	Phe	Ser	Trp	
			100					105					110	•		
His	Asp	Pro	His	Leu	Trp	Arg	Ser	Gly	Asp	Glu	Ala	Pro	Gly	Leu	Phe	
		115					120	٠.				125			٠	
Phe	Val	Asp	۸la	Glu	Arg	Val	Pro	Cys	Arg	His	Asp	Asp	Val	Phe	Phe	
	130					135					140	••	•			
Pro	Pro	Ser	Ala	Ser	Phe	Arg	Val	Gly	Leu	Gly	Pro	Gly	Ala	Ser	Pro	
145					150					155					160	
Val	Arg	Val	Arg	Ser	Ile	Ser	Ala	Leu	Gly	Arg	Thr	Phe	Thr	Arg	Asp	
				165					170					175	•	-
Glu	Asp	Leu	Ala	Val	Phe	Leu	Ala	Ser	Arg	Ala	Gly	Arg	Leu	Arg	Phe	
			180					185				•	190		. 1	• •
His	Gly													Asp		
	!	195	: •	•	•		200	• .		. •	•	205	٠.,	•		
Ser	Gly												•	Cys		•
	210	\$ *			- 4	215	••		••		220	1	. •		• '	
Δla	1 611	וום 1	Gln	Pro	Leu	G1 v	Glv	Are	Cvs	Pro	Gln	Ala	Ala	Cys	His	

225				. :	230	٠.				235		•		, •	240
Ser	Ala	Leu	Arg	Pro	Gln	Gly	Gln	Cys	Cys	Asp	Leu	Cys	Gly	Ala	Val
				245			•		250				٠.	255	:
Val	Leu	Leu	Thr	His	Gly	Pro	Ala	Phe	Asp	Leu	Glu	Arg	Tyr	Arg	Λla
			260					265					270		
Arg	Ile	Leu	Asp	Thr	Phe	Leu	Gly	Leu	Pro	Gln	Tyr	His	Gly	Leu	Gln
		275					280					285			
Val	Ala	Val	Ser	Lys	Val	Pro	Arg	Ser	Ser	Arg	Leu	Arg	Glu	Ala	Asp
	290					295					300				
Thr	Glu	Ile	Gln	Val	Val	Leu	Val	Glu	Asn	Gly	Pro	Glu	Thr	Gly	Gly
305					310					315					320
Ala	Gly	Arg	Leu	Λla	Arg	Ala	Leu	Leu	Ala	Asp	Val	Ala	Glu	Asn	Gly
				325					330				·	335	
Glu	Ala	Leu	Gly	Val	Leu	Glu	Ala	Thr	Met	Arg	Glu	Ser	Gly	Ala	His
			340					345				÷	350		
Val	Trp	Gly	Ser	Ser	Ala	Ala	Gly	Leu	۸la	Gly	Gly	Val	Ala	Ala	Ala
		355					360					365			. •
Val	Leu	Leu	Ala	Leu	Leu	Val	Leu	Leu	Val	Ala	Pro	Pro	Leu	Leu	Arg
	370					375					380				
Arg	Ala	Gly	Arg	Leu	Arg	Trp	Arg	Arg	His	Glu	Ala	Ala	Ala	Pro	Ala
385					390					395				.·	400
Gly	Ala	Pro	Leu	Gly	Phe	Arg	Asn	Pro	Val	Phe	Asp	Val	Thr	Ala	Ser
				405					410				· •,	415	: •
Glu	Glu	Leu	Pro	Leu	Pro	Arg	Arg	Leu	Ser	Leu	Val	Pro	Lys	Ala	Ala
	CO.		420		٠.	,		425				e To	430	, ;	<i>:</i>

Ala	Asp	Ser	Thr	Ser	His	Ser	Tyr	Phe	Val	Asn	Pro	Leu	Phe	Ala	Gly	•	
	:	435		٠,	•	•	440		٠	. •		445			* •		
Ala	Glu	Ala	Glu	Ala													
	450	•					٠				•			•		٠.	
								ŧ									
<210)> 12	26			•										,	. •	
<21	1> 59	9		•										•			
<212	2> PI	RT		•							•			. •			
<213	3> H	omo :	sapi	ens													
<406	0> 1:	26									·			:			•
Met	Thr	Ser	Val	Ser	Thr	Gln	Leu	Ser	Leu	Val	Leu	Met	Ser	Leu	Leu		
ì	•			5					10					15		,	
Leu	Val	Leu	Pro	Val	Val	Glu	Ala	Val	Glu	Ala	Gly	Asp	Ala	lle	Ala		
			20					25		•		٠.	30				• •
Leu	Leu	Leu	Gly	Val	Val	Leu	Ser	Ile	Thr	Gly	Ile	Cys	Ala	Cys	Leu		
		35					40					45	•	,	* *	•	
Gly	Val	Tyr	Ala	Arg	Lys	Arg	Asn	Gly	Gln	Met							
	50					55	•							· • '	., ,		,
															1.		
<21	0> 1	27	• .						•					٠.	÷	•	
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7	hr	Leu	Ser	Ser		Leu												
		: · . ·	•		320					325	٠	,		•	330	N ,	•	
						agc												1120
(Cys	Leu	Asp	Leu	Lys	Ser		٠.		. •	•	• •		. •	1	;	• • •	
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· · · · 10 · · · · · · 15 · · · · · · · · · 20 · · · · · ·	
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⟨213⟩ Homo sapiens

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Ala	Met	Trp	Glu	Asp	Tyr	Glu	Phe	Lys	Cys	Lys	Pro	Gly	Asp	Pro	Ser	•	
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Leu	Ala	His	Asn	Pro	Phe	Ala	Gly	Arg	Pro	Pro	Pro	Arg	Trp	Val	Arg	,,	
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Met Ala Glu

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Asn	Gly	Lys	Asn	Cys	Asp	Gln	Arg	Arg	Val	۸la	Met	Asn	Lys	Glu	His	٠	
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• WO 01/12660 PCT/JP00/05356

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Lys Thr Lys					
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Cys	Cys	Asp	Leu	Cys	Gly	Ala	Val	Val	Leu	Leu	Thr	His	Gly	Pro	Ala		
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Phe	Asp	Leu	Glu	Arg	Tyr	Arg	Ala	Arg	Ile	Leu	Asp	Thr	Phe	Leu	Gly		
265			٠		270		•		•	275					280	•	~
ctg	cct	cag	tac	cac	ggg	ctg	cag	gtg	gcc	gtg	tcc	aag	gtg	cca	cgc		918
Leu	Pro	Gln	Tyr	His	Gly	Leu	G1n	Val	Ala	Val	Ser	Lys	Val	Pro	Arg		
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tcg	tcc	cgg	ctc	cgt	gag	gcc	gat	acg	gag	atc	cag	gtg	gtg	ctg	gtg		966
Ser	Ser	Arg	Leu	Arg	Glu	Ala	Asp	Thr	Glu	Ile	Gln	Val	Val	Leu	Val		
			300			٠	•	305					310	ı			
σ2 σ	aat	aaa	ccc	gag	aca	ggc	gga	gcg	ggg	CZZ	ctg	gcc	Cgg	gcc	ctc		1014
Glu	Asn	•	Pro	Glu	Thr	-	_	Ala	GIY	Arg	Leu		Arg	AIA.	Leu		
•		315				•	320			•	, ,	325	٠			. `	
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Leu	Ala	Asp	Val	Ala	Glu	Asn	Gly	Glu	Ala	Leu	Gly	Val	Leu	Glu	Ala		
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acc	atg	cgg	gag	tcg	ggc	gca	cac	gtc	tgg	ggc	agc	tcc	gcg	gct	ggg		1110
Thr	Met	Arg	Glu	Ser	Gly	Ala	His	Val	Trp	Gly	Ser	Ser	Ala	Ala	Gly		
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ctg	gcg	ggc	ggc	gtg	gcg	gct	gcc	gtg	ctg	ctg	gcg	ctg	ctg	gtc	ctg		1158
Leu	Ala	Gly	Gly	Val	Ala	Ala	Ala	Val	Leu	Leu	Ala	Leu	Leu	Val	Leu		
				365					370					375			
												-+-	0.55	+ 00	. 0 4 4		1206
					ctg												1200
Leu	Val	Ala	Pro	Pro	Leu	Leu	Arg	Arg			•				Arg	•	
	•		380					385		. • •	t		390	• •	* * * *	•	
agg	cac	gag	gcg	gcg	gcc	ccg	gct	gga	gcg	ccc	ctc	ggc	ttc	cgc	aać		1254

BRIGHTONIN- MAIO - NELSERARS I

Arg His Glu Ala Ala Ala Pro Ala Gly Ala Pro Leu Gly Phe Arg Asn	
395 400 405	
ccg gtg ttc gac gtg acg gcc tcc gag gag ctg ccc ctg ccg cgg cgg 130	12
Pro Val Phe Asp Val Thr Ala Ser Glu Glu Leu Pro Leu Pro Arg Arg	
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Leu Ser Leu Val Pro Lys Ala Ala Asp Ser Thr Ser His Ser Tyr	
425 430 435 440	
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Phe Val Asn Pro Leu Phe Ala Gly Ala Glu Ala Glu Ala	
445 450	
ctgaccgtcg accttggggc tctccaccc ctctggcccc agtcgaactg ggggctagcc 146	0
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	Met Thr Sei	r Val Ser Thr Gln Leu	
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tcc tta gtc ctc atg tca ct	g ctt ttg gtg ctg	cct gtt gtg gaa gca	222
Ser Leu Val Leu Met Ser Le	u Leu Leu Val Leu	Pro Val Val Glu Ala	
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Val Glu Ala Gly Asp Ala Il	e Ala Leu Leu Leu	Gly Val Val Leu Ser	
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Ile Thr Gly Ile Cys Ala Cy	s Leu Gly Val Tyr	Ala Arg Lys Arg Asn	
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Gly Gln Met			<i>:</i>
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gcct	ggad	ag o	egeet	gctg	gc co	egect	tcccg	gate	g gco	cte	g ccc	cag	gate	g tgi	t gac	174
								Met	. Ala	a Leu	ı Pro	Glr	n Mei	t Cys	s Asp	
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Gly	Ser	His	Leu	Ala	Ser	Thr	Leu	Arg	Tyr	Cys	Met	Thr	Val	Ser	Gly	
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Gly	Asp	Ala	Thr	Ala	Gln	Pro	Gly	Gln	Leu	Ala	Pro	Pro	Thr	Glu	Tyr	
	٠.,	e sa j	, •	45			٠.	, .	-50	_		-		- 55	• • • •	
ccg	gtg	cct	gag	ggc	ccc	agc	ccc	ctg	ctc	agg	tcc	gtc	agc	ttc	gtc	366
Pro	Val	Pro	Glu	Gly	Pro	Ser	Pro	Leu	Leu	Arg	Ser	Val	Ser	Phe	Val	

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;	120					•	115					110				•	105
∵558	gtg	gcc	gaa	gag	ac i	t	act	ссс	atc	gac	gtt	gtg	aaa	ccc	acc	agg	tgc
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	Thr	Pro	уr	la	ro A	P	Pro	Thr	Pro	Pro	Gly	Glu	Ala	Val	Pro	Phe	Ser
•		•'	50						145	•				140			
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	Thr	Ser	.eu	.eu	la I	A.	Asp	Arg	Ser	Gly	Ser	Pro	Glu	Leu	Λla	Glu	Glu
٠.				65	1			•		160		:	•		155		
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•	.,	, .			80	18					175	•	٠.			170	
750	tca	tgc	cc	gc	ca c	a	gcc	agt	ccg	aca	acg	gag	gca	tct	gtt	gcc	gat
	Ser	Cys -	er	rg	nr A	Tŀ	Ala	Ser	Pro	Thr	Thr	Glu	Ala	Ser	Val	Ala	Asp
,	200	j.\$	٠. ,				195				. : 	.190.	٠.,	:			185

∵.

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Gly Leu Val Gln Thr Ala Arg Gly Gly Ser	
205 210	
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Arg Arg Phe Leu Leu Pro Asp Ala Glu Ala Gln Leu Asp Arg Glu	•
15 20 25	
ggt gac gcc ggg ccg gaa acc tcc aca gct gtt gag aaa aag gag aaa	148
Gly Asp Ala Gly Pro Glu Thr Ser Thr Ala Val Glu Lys Lys Glu Lys	
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	106

Pro	Leu	Pro	Arg	Leu	Asn	Ile	His	Ser	Gly	Phe	Trp	Ile	Leu	Ala	Ser	• •	
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att	gtt	gtg	acc	tat	tat	gtt	gac	ttc	ttt	aaa	acc	ctt	aaa	gaa	aac		244
Ile	Val	Val	Thr	Tyr	Tyr	Val	Asp	Phe	Phe	Lys	Thr	Leu	Lys	Glu	Asn		
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ttc	cac	act	agc	agc	tgg	ttt	ctc	tgt	ggc	agt	gcc	ttg	ttg	ctt	gtc	• • •	292
Phe	His	Thr	Ser	Ser	Trp	Phe	Leu	Cys	Gly	Ser	Ala	Leu	Leu	Leu	Val		
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Ser	Leu	Ser	Ile	Ala	Phe	Tyr	Cys	Ile	Val	Tyr	Leu	Glu	Trp	Tyr	Cys		
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gga	att	gga	gaa	tat	gat	gtc	aag	tat	cca	gcc	ttg	ata	ccc	att	acc		388
Gly	Ile	Gly	Glu	Tyr	Asp	Val	Lys	Tyr	Pro	Ala	Leu	Ile	Pro	Ile	Thr		
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Thr	Ala	Ser	Phe	Ile	Ala	Ala	Gly	Ile	Cys	Phe	Asn	Ile	Ala	Leu	Trp	•	
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His	Val	Trp	Ser	Phe	Phe	Thr	Pro	Leu	Leu	Leu	Phe	Thr	Gln	Phe	Met		
140	,		•		145	•				150					155		
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Gly	Val	Val	Met	Phe	Ile	Thr	Leu	Leu	Gly					:	•	•••	
	٠.		•	160			. •		165	•							
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tca	gcct	tcg	aagt	agtt	gg g	acta	cagg	с сс	acgc	cacc	gtg	cctg	gct	ggac	atgt	aa	650

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aggaag atg c	tc cag acc	agt aac ta	ac ago ctg	gtg ctc tct	ctg cag	228
Met L	eu Gln Thr	Ser Asn Ty	yr Ser Leu '	Val Leu Ser	Leu Gln	

ttc	ctg	ctg	ctg	tcc	tat	gac	ctc	ttt	gtc	aat	tcc	ttc	tca	gaa	ctg	, *	276
Phe	Leu	Leu	Leu	Ser	Tyr	Asp	Leu	Phe	Val	Asn	Ser	Phe	Ser	Glu	Leu		
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ctc	caa	aag	act	cct	gtc	atc	cag	ctt	gtg	ctc	ttc	atc	atc	cag	gat		324
Leu	Gln	Lys	Thr	Pro	Val	Ile	Gln	Leu	Val	Leu	Phe	Ile	Ile	Gln	Asp		
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Ile	Ala	Val	Leu	Phe	Asn	Ile	Ile	Ile	Ile	Phe	Leu	Met	Phe	Phe	Asn		
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acc	ttc	gtc	ttc	cag	gct	ggc	ctg	gtc	aac	ctc	cta	ttc	cat	aag	ttc	•	420
Thr	Phe	Val	Phe	Gln	Ala	Gly	Leu	Val	Asn	Leu	Leu	Phe	His	Lys	Phe		
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Lys	Gly	Thr	Ile	Ile	Leu	Thr	Ala	Val	Tyr	Phe	Ala	Leu	Ser	Ile	Ser		
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Leu	His	Val	Trp	Val	Met	Asn	Leu	Arg	Trp	Lys	Asn	Ser	Asn	Ser	Phe		
95					100					105					110		
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Ile	Trp	Thr	Asp	Gly	Leu	Gln	Met	Leu	Phe	Val	Phe	Gln	Arg	Leu	Ala	•	
-				115	•				120	ı				125	;		
gca	gtg	ttg	tac	tgc	tac	ttc	tat	aaa	cgg	aca	gcc	gta	aga	cta	ggc		612
Ala	Val	Leu	Tyr	Cys	Tyr	Phe	Tyr	Lys	Arg	Thr	Ala	·Val	Arg	g Leu	Gly		
	•		130)				135	•				140)			
ast	cct		++-	ten	- പ്ര	gar	tet	: tto	tee	cte	CEC	aas	gas	tto	atg		660

180

305/307

Asp Pro Hi	s Phe Tyr G	ln Asp Ser	Leu Trp Leu	Arg Lys Glu	ı Phe Met	
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caa gtt cg	a agg tgacc	tct tgtcaca	ctg atggata	ctt tteette	ctg	710
Gln Val Ar	g Arg					
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231		tg :	g ct	g go	g go	g tt	g go	gʻtt	g go	c at	gcgc	g ct	gccg	tgct	cc c	gctt	ctct
		eu į	a Le	a Al	eu Al	a Le	eu Al	la Le	et Al	Ме			•				
:					5 ·				1			•	•				
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.*					85					80					75		
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•				٠.	٠	100					95					90	
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	1	Leu	Met	Phe	Ile	Gly	Asp	Asn	Gly	Ile	Arg	Leu	Gln	Asp	Ala	Asp	Asp
)	120	٠.	<u>.</u>			115		٠	. •		110					105
615	-	tct	ctg	ttc	ttt	222	att	too	aac	ttt	ctc	ttc	gea.	atσ	ttc	itt	act

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Thr	Phe	Phe	Met	Ala	Phe	Leu	Phe	Asn	Тгр	Ile	Gly	Phe	Phe	Leu	Ser	
				125					130					135		
ttt	tgc	ctg	acc	act	tca	gct	gca	gga	agg	tat	ggg	gcc	att	tca	gga	663
Phe	Cys	Leu	Thr	Thr	Ser	Ala	Ala	Gly	Arg	Tyr	Gly	Ala	Ile	Ser	Gly	
			140					145					150			
ttt	ggt	ctc	tct	cta	att	aaa	tgg	atc	ctg	att	gtc	agg	ttt	tcc	acc	711
Phe	Gly	Leu	Ser	Leu	Ile	Lys	Trp	Ile	Leu	Ile	Val	Arg	Phe	Ser	Thr	
	,	155					160					165				
tat	ttc	cct	gga	tat	ttt	gat	ggt	cag	tac	tgg	ctc	tgg	tgg	gtg	ttc	759
Tyr	Phe	Pro	Gly	Tyr	Phe	Asp	Gly	Gln	Tyr	Trp	Leu	Trp	Trp	Val	Phe	
	170					175					180					
ctt	gtt	tta	ggc	ttt	ctc	ctg	ttt	ctc	aga	gga	ttt	atc	aat	tat	gca	807
Leu	Val	Leu	Gly	Phe	Leu	Leu	Phe	Leu	Arg	Gly	Phe	Ile	Asn	Tyr	Ala	
185					190					195					200	
aaa	gtt	cgg	aag	atg	cca	gaa	act	ttc	tca	aat	ctc	ccc	agg	acc	aga	855
Lys	Val	Arg	Lys	Met	Pro	Glu	Thr	Phe	Ser	Asn	Leu	Pro	Arg	Thr	Arg	
				205					210		•			215		
gtt	ctc	ttt	att	tat	taa	agat	gtt	ttct	ggca	aa g	gcct	tcct	g ca	ttta	tgaa	910
Val	Leu	Phe	Ile	Tyr					•				•			
			220													
ttc	tctc	tca	agaa	gcaa	ga g	aaca	cctg	c ag	gaag	tgaa	tca	agat	gca	gaac	acagag	970
gaa	taat	cac	ctgc	ttta	aa a	aaat	aaag	t ac	tgtt	gaaa	ag					1012

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(54) Title: HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAs ENCODING THESE PROTEINS

(57) Abstract: The present invention provides human proteins having hydrophobic domains. DNAs encoding these proteins, expression vectors for these DNAs, transformed eukaryotic cells expressing these DNAs and antibodies directed to these proteins.

INTERNATIONAL SEARCH REPORT

International Application No PC1, JP 00/05356 STAGE WOLLS A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C12N1/21 C12N5/10 C07K14/47 - C07K16/18 According to International Patent Classification (IPC) or to both national classification and IPC Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12N C07K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) STRAND, MEDLINE C. DOCUMENTS CONSIDERED TO BE RELEVANT Category ° Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. WO 99 13074 A (TSURITANI KATSUKI ;YAZAKI Х 1-7 MADOKA (JP); MATSUMOTO KAYO (JP); TAISHO) 18 March 1999 (1999-03-18)
SEQ ID NO:1 is 100% identical to SEQ ID
NO:1 of present application figure 5 Х Further documents are listed in the continuation of box C. Patent family members are listed in annex. * Special categories of cited documents : "I later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance invention "E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu-"O" document referring to an oral disclosure, use, exhibition or ments, such combination being obvious to a person skilled in the art. other means "P" document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 19.02.01 27 November 2000

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European Patent Office, P.B. 5818 Patentiaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, INTERNATIONAL SEARCH REPORT

PCT/JP 00/05356

Box I	Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)
This Inte	ernational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1.	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2.	Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
-	
з. 🗌	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This Inte	rnational Searching Authority found multiple inventions in this international application, as follows:
	see additional sheet
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
з	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. X	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1 - 7 (all partially)
Remark	on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Claims: Invention 1: Claims 1-7 (all partially)

Polypeptide comprising an amino acid sequence as in SEQ ID NO:1 and subject-matter relating thereto. Polynucleotides encoding the polypeptide of SEQ ID NO:1 such as a polynucleotide comprising a polynucleotide sequence as in SEQ ID NO:11 (coding sequence) or a polynucleotide consisting of a polynucleotide sequence as in SEQ ID NO: 21 (complete cDNA sequence) and subject-matter relating thereto.

2. Claims: Invention 2-50: Claims 1-7 (all partially)

Idem as subject 1 but limited to each of the polypeptides as in SEQ ID NOs:2-10, 31-40, 61-70, 91-100 and 121-130 and polynucleotides as in SEQ ID NOs:12-20, 41-50, 71-80, 101-110, 131-140 and SEQ ID NOs:22-30, 51-60, 81-90, 111-120 and 141-150, respectively. Invention 2 is limited to subject-matter relating to SEQ ID NOs:2 (protein), 12 (coding sequence) and 22 (complete cDNA), invention 3 to SEQ ID NOs 3, 13 and 23, etc.



INTERNATIONAL SEARCH REPORT

ormation on patent family members

International Application No PC1/JP 00/05356

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9913074	18-03-1999	AU 8999298 A JP 11151096 A	29-03-1999 08-06-1999

Form PCT/ISA/210 (patent family annex) (July 1992)

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